American Academy of Allergy, Tenth Annual Meeting, Shamrock Hotel, Houston, Texas, February 1, 2, 3, 1954.

UNIVERSITY OF MICHIGAN
FEB 3 1954
MEDICAL LIBRARY
DOES NOT CIRCULATE

The Journal of Allergy

Official Organ of AMERICAN ACADEMY OF ALLERGY

Including ALLERGY ABSTRACTS

CONTENTS FOR JANUARY, 1954

Original Articles

Studies on Factors Influencing Ragweed Pollen Counts in the New York Metropolitan District. I. Pollen Studies on Ambrose Lightship in New York Harbor. Richard D. Wiseman, M.D., S. Senior Sack, M.D., Bernard B. Siegel, M.D., Israel Glazer, M.D., and Matthew Walzer, M.D., Brooklyn, N. Y. ---------- 1

Fractionation of Ragweed Antigens by the Use of Ion Exchange Resins. Ralph Bookman, M.D., and Harry Wax, Ph.D., Los Angeles, Calif. ---------- 12

Latent Atopy and the Incidence of the Atopic State. Sheppard Siegal, M.D., and Thomas Seideman, M.D., New York, N. Y. ---------- 20

(*Contents Continued on Page 2*)

Vol. 25, No. 1 JANUARY, 1954

PUBLISHED BI-MONTHLY BY THE C. V. MOSBY CO., ST. LOUIS 3, MO.

which patient has "off-season" allergy?

One – or both – may have, if "allergy is perhaps the commonest cause of a stuffy nose . . ."[1]
In dealing with "off-season" allergy consider the advantages of Pyribenzamine, demonstrated in thousands of reported cases:

Prompt and prolonged relief of allergic "stuffy" nose.

Effective control of rhinorrhea and sneezing.

A notable lack of sedation and other unfavorable reactions.

Pyribenzamine hydrochloride
(tripelennamine hydrochloride Ciba)
Supplied as 50-mg. tablets,
in bottles of 100 and 1000.

1. Dill, J. L.: Postgrad. Med. 4:413, 1948.

Ciba Pharmaceutical Products, Inc., Summit, New Jersey

Pyribenzamine®

no other antihistamine combines greater clinical benefit with greater freedom from side effects

Ciba

2/1887M

Medical
Taxon

610.5
J86
A43
v.25

The Journal of Allergy

VOL. 25 JANUARY, 1954 No. 1

Original Articles

STUDIES ON FACTORS INFLUENCING RAGWEED POLLEN COUNTS IN THE NEW YORK METROPOLITAN DISTRICT

I. POLLEN STUDIES ON AMBROSE LIGHTSHIP IN NEW YORK HARBOR*

RICHARD D. WISEMAN, M.D., S. SENIOR SACK, M.D., BERNARD B. SIEGEL, M.D., ISRAEL GLAZER, M.D., AND MATTHEW WALZER, M.D., BROOKLYN, N. Y.

SINCE 1936, the Allergy Division of the Jewish Hospital of Brooklyn has been making daily estimates of the ragweed pollen content of the air in and about New York City. During the first ten years, the air was sampled by the exposure of greased slides in a crude shelter on the roof of the hospital. The adoption, in 1946, of the Durham Shelter as a standard instrument of exposure and the standardization of counting techniques by the Pollen Committee of the Research Council of the American Academy of Allergy[1, 2] made more intensive studies[3, 4, 5] of New York City's pollen problems feasible.

Since 1946, surveys have been made during the ragweed pollinating seasons for one or more years in about 20 localities in the city and its environs. In some years, as many as 17 stations in the Metropolitan District† were studied. At the same time, meteorologic data from weather stations in these areas were analyzed in an attempt to correlate weather factors with pollen counts.

Almost coincidentally with the start of these surveys, the New York City Department of Health initiated a program of ragweed plant eradication within the city. This prompted considerable speculation as to the extent to which such an intramural campaign would influence pollen counts in the city and benefit its hay fever sufferers. It was common knowledge that ragweed pollen was wind-borne and could be carried from distant regions of heavy pollination into areas where ragweed growth was scant or absent. Durham, more than two decades ago, had suggested that New York City was probably receiving much of its pollen from the large ragweed beds in New Jersey.[6] However, concrete data on these questions were lacking, a circumstance which prompted the writers to enter upon more extensive studies of these problems as soon as the standard technique became available.

From the Allergy Division of The Jewish Hospital of Brooklyn.
Presented at a meeting of The New York Allergy Society, April 26, 1950.
Received for publication Sept. 16, 1953.
*Aided by a grant from the Celia G. Antonoff Research Fund.
†The New York City Metropolitan District encompasses the area within a 50-mile radius of Columbus Circle at Broadway and 59th St., New York City.

In 1947, the second year of surveys of the Metropolitan District, a study was made of ragweed pollen conditions at Fire Island, N. Y.[4] (Fig. 1, Station K). Because this island was relatively free of ragweed plants and was situated in the Atlantic Ocean several miles south of Long Island, it was frequently mentioned by the laity as a haven for hay fever patients sensitive to ragweed. Our studies revealed that while Fire Island tended to show daily ragweed pollen counts somewhat lower than the daily average for Greater New York, there were several days early in September, 1947, when readings on the island exceeded the city averages. Although the seasonal total* of 298 at Fire Island was relatively low, it exceeded the seasonal total of 271 for the borough of Brooklyn (Fig. 1, Station B) in New York City for that year and was approximately 70 per cent of the average total* of 423 for New York City.

The study of this problem was continued in 1948 and 1949 by a survey[5] of ragweed pollen conditions at Sandy Hook, N. J. (Fig. 1, Station J). This area presented unusual characteristics in that it was a narrow peninsula, not more than a few hundred yards wide, extending several miles into the ocean with only a scant growth of ragweed plants. Despite these features which would be expected to produce low counts, the seasonal total for Sandy Hook in 1948 was 563, as compared to an average total of 530 for New York City. In 1949, the seasonal totals for Sandy Hook and New York City (average) were 494 and 550, respectively.

The data obtained in the Fire Island and Sandy Hook surveys clearly indicated that the peak counts in these areas of scant ragweed growth occurred on those days during the active pollinating period when winds blew briskly from the west. In this direction, according to previous surveys, were located the areas of densest ragweed growth in and around the New York metropolitan area.

The study of wind as a factor in New York's pollen problem continued under more ideal experimental conditions during the summers of 1949 and 1950 when pollen counts were made at Ambrose Lightship, anchored far out in the bay at the entrance to New York Harbor (Fig. 1, Station A). Here the absence of ragweed plants was complete and all pollen granules appearing on the exposed slides were incontrovertibly wind-borne from neighboring land areas.

The cooperation of the Aids to Navigation Division of the United States Coast Guard was enlisted to effect the surveys on Ambrose Lightship. The daily counts obtained on the ship were correlated with those obtained at the land stations (Table I) in the New York Metropolitan District during the same seasons.

These surveys yielded striking evidence that wind direction and velocity were the most significant meteorologic factors influencing the city's daily ragweed pollen counts. An analysis of the data obtained in annual surveys from

*The seasonal total for a station is computed by totaling its daily counts from August 1 through September 30 in terms of pollen granules per square centimeter of exposed slide per twenty-four hours. The average total for New York City represents the average of the seasonal totals of the five city boroughs.

1936 to 1946, with the counting technique employed before standard procedures were established, substantiated these conclusions. A detailed analysis of the evidence provided by these earlier studies will be the subject of another communication in this series.

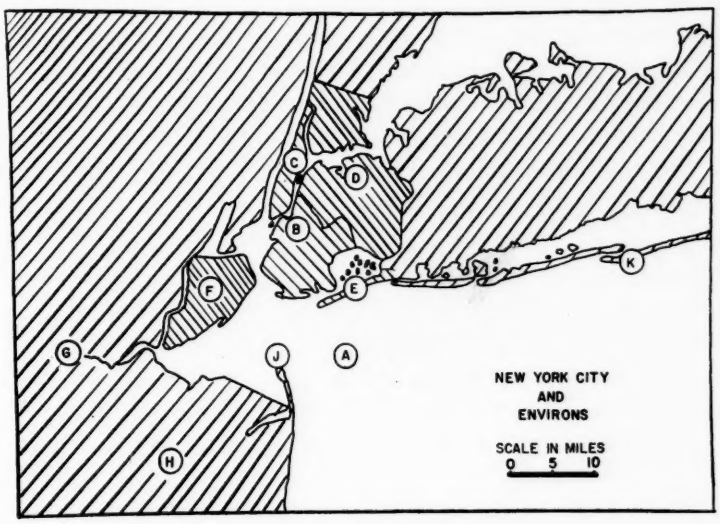


Fig. 1.—Localities surveyed in and around New York City. The locations of the stations, indicated by the encircled letters, are listed in Table I.

Location of Ambrose Lightship.—Ambrose Lightship (Station A) is anchored at the entrance to New York Harbor. Its approximate location and land relationships are illustrated in Fig. 1. The nearest land to the north of the Lightship is the Rockaway Peninsula (Station E) in New York at a distance of 8 or 9 miles. Equidistant to the west lies Sandy Hook, New Jersey (Station J). The Atlantic Ocean stretches to the south and east, so that from these directions, representing about one-third of its circumference, the ship can receive no pollen. To the west and southwest lies New Jersey, represented in the survey by the counting stations at New Brunswick (Station G) and Marlboro (Station H). In previous surveys, the pollen counts in this section of New Jersey had been found to be the highest in the New York Metropolitan District. West and slightly north of the Lightship lies Staten Island (Station F) with moderately high pollen counts, and northern New Jersey, with counts approximating the average for New York City. To the north and slightly west are Brooklyn (Station B) and Manhattan (Station C), with unimpressive counts. Due north lies the borough of Queens (Stations D and E) and, east of it, western Long Island, parts of which had been surveyed in previous years. With the exception of Rockaway (Station E), no stations on any part of Long Island had shown unusually high counts at any time during these surveys.

Techniques.—The technique employed conformed with the recommendations of the Pollen Survey Committee of the Research Council of the American

Academy of Allergy. Greased slides were exposed on a Durham Shelter fastened to the railing on the upper deck of the Lightship at a point as distant as possible from the smokestack. Slides were changed each day at 9 A.M. Daylight Saving Time (8 A.M. Eastern Standard Time) from August 1 through September 30.

A portion of the exposed greased slide was stained with Calberla's solution and a cover slip with an area of 3.6 sq. cm. was applied. After about ten minutes, the ragweed pollen grains under the cover slip were counted and recorded in terms of the number of granules collected on a square centimeter of slide in twenty-four hours. On rainy days, the counts, though incomplete, were recorded. They appear on the graphs as points enclosed in circles.

Daily data on wind velocity and prevailing wind direction, as recorded at the Battery in New York City and at Trenton, N. J., were obtained from the United States Department of Commerce Weather Bureau. Readings were also obtained from other weather stations in the Metropolitan area located at Central Park, Manhattan, at LaGuardia and Idlewild Airports in Queens, at Sandy Hook and Newark Airport in New Jersey, and at Ambrose Lightship. These readings corresponded so closely with those obtained at the Battery that it was decided, for the sake of uniformity and convenience, to use only the data obtained at the latter station.

TABLE I. SEASONAL TOTALS* OF RAGWEED POLLEN

STATION	LOCATION	1949	1950
A.	Ambrose Lightship	256	249
B.	Jewish Hospital of Brooklyn	395	224
C.	United States Weather Bureau, Central Park, Manhattan	481	227
D.	Chamber of Commerce Building, Flushing, Queens	560	500
E.	Rockaway Beach Hospital, Queens	990	638
F.	Sea View Hospital, Staten Island	714	458
	NEW YORK CITY AVERAGE	550	420
G.	St. Peter's General Hospital, New Brunswick, N. J.	1,313	957
H.	New Jersey State Hospital, Marlboro, N. J.	937	—
J.	United States Coast Guard Weather Station, Sandy Hook, N. J.	494	—
K.	United States Coast Guard Weather Station, Fire Island, N. Y. (surveyed in 1947)		

*Seasonal totals for each station are obtained by adding all its daily counts which are in terms of pollen granules per square centimeter of slide, exposed for twenty-four hours.

The daily readings for average wind velocity and prevailing wind direction, which are published by the Weather Bureau, are based on the averages of twenty-four hourly readings starting at midnight. The pollen slides, however, were exposed for twenty-four hours starting at 9 A.M. In order to correlate the pollen count and weather data for each day, it became necessary to recompute from the hourly readings, the daily average wind velocity and prevailing wind direction so that the twenty-four hour period covered corresponded to that of the pollen slide exposures. It was also necessary at times to analyze the hourly readings for wind velocity and wind direction in order to account for unusual pollen counts on the Lightship which could not be explained on the basis of the reported *average* wind readings for that day.

Results of Studies During the 1949 Ragweed Season.—The seasonal totals for ragweed obtained at the representative stations surveyed in 1949 are listed in Table I. It will be noted that the lowest seasonal total in the survey was 256 which was obtained at the Ambrose Lightship. This figure was approximately 46 per cent of the average of the seasonal totals of all the New York City stations (550). As in previous years, the highest seasonal totals in the Metropolitan area were those of Marlboro and New Brunswick, representing that part of New Jersey which lies west and southwest of the Lightship. Rockaway, with a seasonal total of 990, was the only station in New York City with pollen counts comparable in intensity to those found in this section of New Jersey.

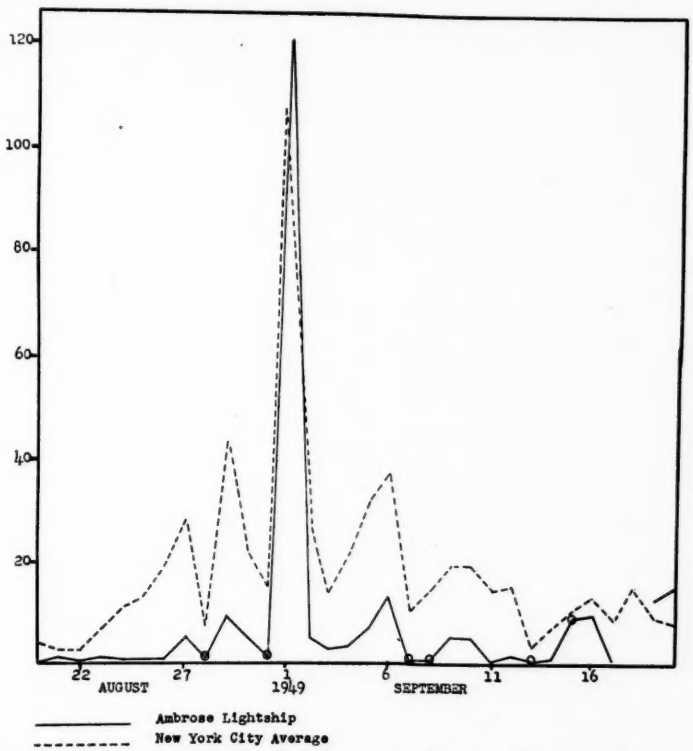


Fig. 2.—Graphs represent daily pollen counts at the Ambrose Lightship and the daily averages for New York City during the 1949 ragweed season. Circles indicate incomplete counts because of rain.

The daily ragweed pollen counts during the 1949 season at Ambrose Lightship and the stations around it are graphically presented in Figs. 2 and 3. The highest count of the year was recorded at every station, *including the Lightship,* on September 1. This was the only day *during the height of ragweed pollination* when the prevailing wind blew briskly from the west. The wind velocity on that day averaged 19 miles and reached a maximum of 34 miles per hour. These wind conditions were ideal for the transfer of pollen from the districts of high concentration in New Jersey, as represented by counts on that day of 182 at New Brunswick (Fig. 3, *A*) and 142 at Marlboro (Fig. 3, *B*) to the pollen-free

or pollen-poor areas to the east. It was thus possible to account for the imposing readings of 122 and 146 obtained respectively at the Lightship (Fig. 2) and Sandy Hook (Fig. 3, *E*) on that date. Significant is the fact that the count on the Lightship that day exceeded those of all the land stations in New York City with the sole exception of Rockaway (Fig. 3, *F*).

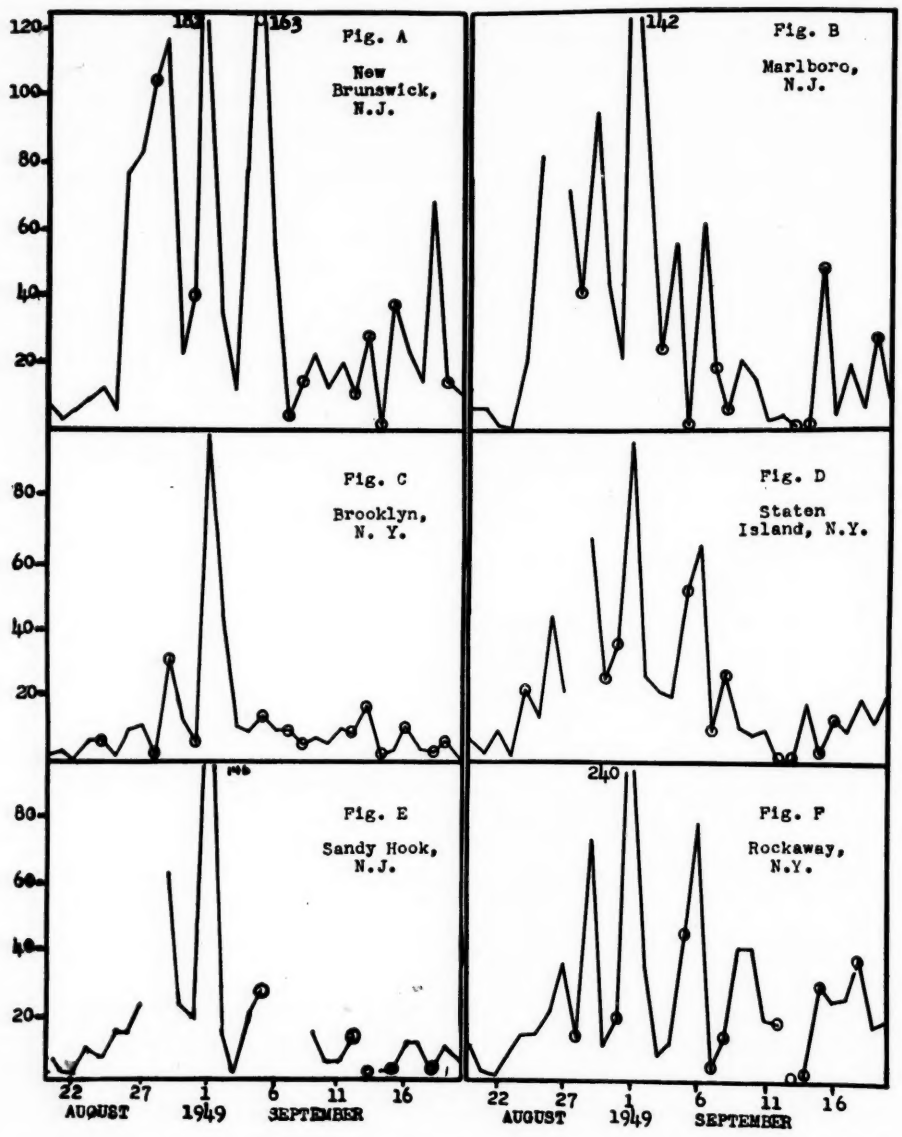


Fig. 3.—Graphs represent daily pollen counts at stations surrounding the Ambrose Lightship during the 1949 ragweed season. The gaps in *B, D. E.* and *F* denote a lack of data.

On September 2, 3, and 4, the prevailing winds in New York City again blew from the southwest. However, the winds were gentle and never exceeded 11 miles per hour. Under these circumstances Ambrose Lightship received only

small amounts of pollen and registered counts of 4, 3, and 4, respectively, on these dates. Although moderately high counts of 104 and 42 were obtained on August 28 at New Brunswick and Marlboro, respectively, the counts on the Lightship that day remained at zero because of a south wind which blew steadily from the ocean. On August 29 and September 6, winds blew with average velocities of 16 to 20 miles per hour toward the Lightship from the northwest, i.e., from the direction of Staten Island. Counts of 68 and 65, respectively, were obtained at Staten Island (Fig. 3, *D*) on these two days. Hence, on the basis of the prevailing wind condition, the counts at the Lightship of 10 and 14 on these two days were readily accounted for.

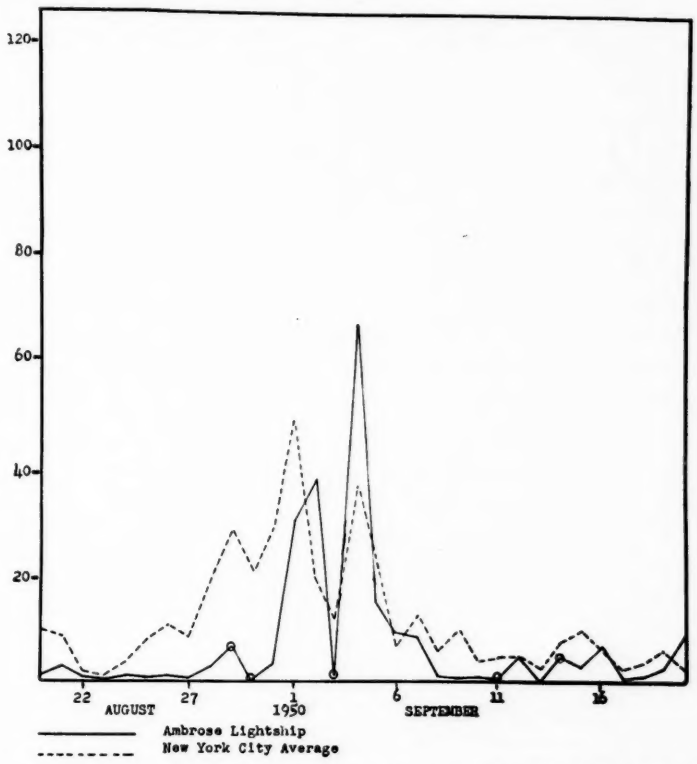


Fig. 4.—Graphs represent daily pollen counts at the Ambrose Lightship and the daily averages for New York City during the 1950 ragweed season.

Results of Studies During the 1950 Ragweed Season.—The ragweed pollen counts at the various stations surveyed in 1950 (Table I) are presented graphically in Figs. 4 and 5. The findings further establish the relationship of wind direction and velocity to the pollen counts on Ambrose Lightship as noted in 1949.

The three peak counts on the Lightship in 1950 occurred on September 1, 2, and 4 (Fig. 4). On September 1 the count at the Lightship was 31. The prevailing wind that day was from the southwest, with an average velocity of 13.8 miles per hour. The reading at New Brunswick that day was 74 (Fig. 5, *A*). The second peak count occurred on September 2 when the average wind

velocity was recorded as 7.8 miles per hour from the northeast. These wind conditions could not account for the high reading on the Lightship, but analysis of the hourly wind figures revealed that from 11 A.M. to 3 P.M. on September 2 there were northern winds ranging up to 13 miles per hour. On this day, the stations to the north of the Lightship, Flushing and Rockaway (Fig. 5, *B*), showed the highest counts in New York City. It thus seems likely that the pollen found on the Lightship slide on September 2 came from the land areas to the north of this station.

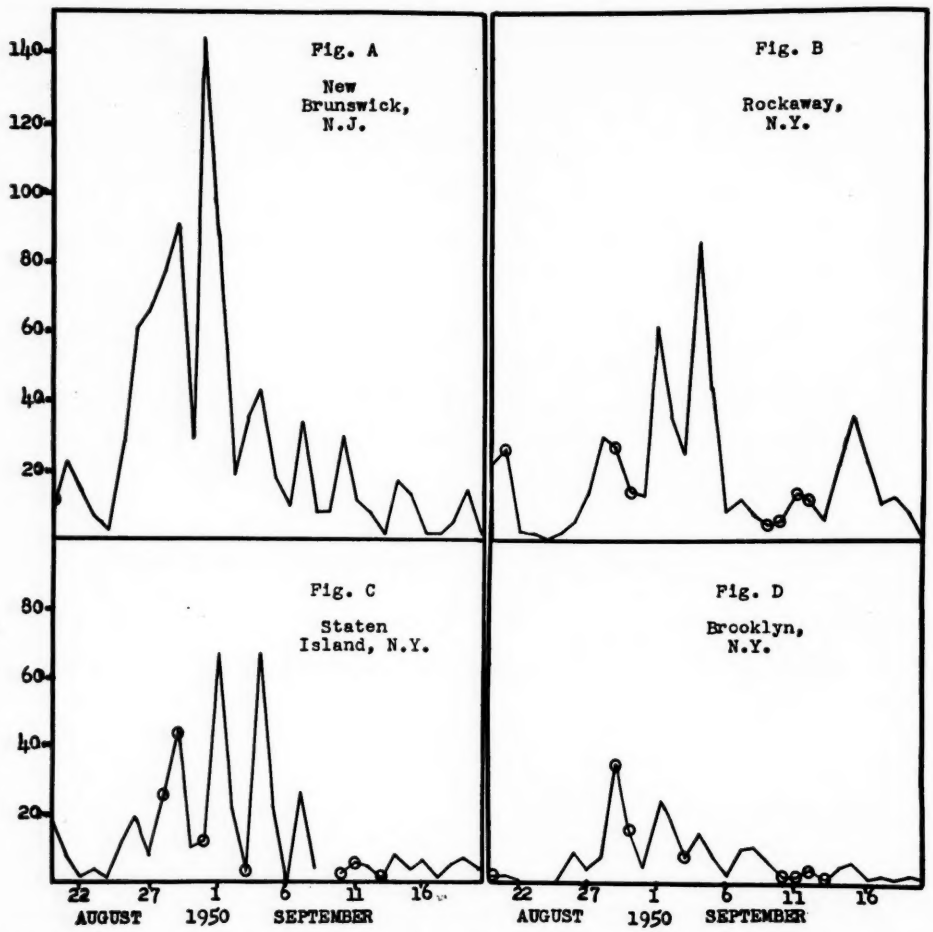


Fig. 5.—Graphs represent daily pollen counts at various localities surrounding the Ambrose Lightship during the 1950 ragweed season.

The highest count at the Lightship in 1950 was the reading of 67 on September 4 (Fig. 4). On that day, the wind was blowing at an average of 19 miles per hour from the northwest, i.e., from the direction of Staten Island, which also registered one of its peak days (Fig. 5, *C*) on this day. Despite high counts at New Brunswick (Fig. 5, *A*) from August 25 to August 31, the counts at the Lightship were low. On these days, the winds were southern most of the time and the occasional land breeze was gentle.

During the 1950 ragweed season, the seasonal total for Ambrose Lightship was 249, which was about 60 per cent of the average seasonal total of 420 for New York City. The seasonal total on the Lightship that year actually exceeded the totals for Brooklyn and for Central Park in Manhattan, which were 224 and 227, respectively (Table I).

DISCUSSION

Ample evidence of the importance of wind-borne pollen as a factor in the pollen problem in the New York City Metropolitan area has been presented. This fact had become evident in our studies on Fire Island in 1947 and on Sandy Hook in 1948 and 1949. Both of these areas have relatively few indigenous ragweed plants. The high readings which were found at these locations usually occurred on days when the winds blew briskly from the west. Though Fire Island is at least 60 miles from New Jersey, the evidence seemed to point to winds blowing from this direction as the bearers of most of the ragweed pollen found on the Island. The capacity of wind to transport ragweed pollen for distances up to 200 miles has been demonstrated by Sack[10] in his controlled studies of slides exposed on planes and ships traversing the Atlantic Ocean.

The data collected in 1949 and 1950 at Ambrose Lightship, which is within the New York Metropolitan District and yet is completely ragweed-free, afforded even more convincing proof of the importance of wind-borne pollen as a factor influencing the city's pollen counts. The Lightship study demonstrated how an area totally free of ragweed plants could, under suitable conditions of wind direction and velocity, become grossly contaminated with large amounts of ragweed pollen. The day most illustrative of this point was Sept. 1, 1949, when the highest count (122) during the two years of the Lightship studies was obtained. On that day, western winds averaging 19 miles per hour brought in considerable amounts of ragweed pollen. It is significant that on this day, on which peak counts were obtained at all New York City stations, the reading at the Lightship actually exceeded some of those in the city boroughs which were producing their own ragweed pollen, but were less affected by the wind currents than the Lightship.

The data obtained in the Ambrose Lightship studies shed considerable light on the benefits which may be anticipated from local ragweed eradication programs such as the one being carried on by the New York City Health Department and by health and civic organizations in other communities. During 1949 and 1950 there were fifteen days during the ragweed seasons when the ragweed pollen count on the Ambrose Lightship was 8 or more granules per square centimeter of exposed slide. Such pollen concentration in the air would be likely to cause symptoms in most untreated ragweed-sensitive patients. Aside from the peak days previously noted, the counts at Ambrose Lightship tended to be lower than the New York City average counts for the same days (Figs. 2 and 4). It is apparent, therefore, that if ragweed plants were completely eradicated from New York City the patients would only be benefited on those days when there were no strong winds with a western component or when winds blew from the south or east.

Since the Lightship is about 9 miles from the nearest land and, in most directions, is at least 13 miles from shore, it may be considered to be situated at the center of an area which is completely free of ragweed plants and, by the most conservative estimate, covers at least 250 square miles.

The results obtained at the Lightship station may serve as an index of what may be expected in any neighboring land area of similar size undergoing ragweed extermination when it is surrounded by areas of heavy ragweed growth. Allowances are to be made for the fact that the Lightship area is exposed to land breezes on only two-thirds of its circumference. If this ragweed-free point were surrounded by land on all sides it is reasonable to assume that its seasonal totals would be considerably higher than those which were recorded. In 1949 and 1950 the seasonal ragweed totals at the Lightship were 46 and 60 per cent, respectively, of the average city totals for the same period. One may therefore speculate that in seasons such as New York City experienced in 1949 and 1950, total eradication of ragweed in a similar 250 square mile area in the city might diminish the seasonal total for the center of that area by about one-half, with diminishing effectiveness as the distance from the center increased. Increases in the number of days with western winds during the height of the pollen season would increase the contamination of the treated area and diminish the benefits of the ragweed elimination campaigns.

It is obvious that any attempt at ragweed extermination which concentrates only upon the elimination of the endogenous ragweed crop in New York City is bound to meet with only limited success. It would appear that ragweed extermination campaigns waged within the limits of New York City hold little promise for pronounced relief to hay fever sufferers unless a thorough and continuous eradication program can be waged for a few hundred miles in every land direction surrounding the city, with particular attention paid to districts west of the city.

The conclusions drawn from these studies support the recommendations of others who have investigated this problem.[11] While the study at the Lightship has dealt with ragweed, the conclusions may be applied to other eradication programs directed against elimination of plants generating windborne pollen. The effectiveness of ragweed elimination campaigns will be the subject of more detailed discussion in a subsequent communication in this series.

CONCLUSIONS

1. Ragweed pollen in considerable amounts was found on slides exposed at Ambrose Lightship in New York Harbor at a point at least 9 miles from the nearest land.

2. Wind direction and wind velocity were the most important determinants of the atmospheric concentration of ragweed pollen on the Lightship, a point entirely free of ragweed plants.

3. In 1949 and 1950 ragweed seasons, during which there were only two or three days at the height of ragweed pollination each season when strong

western winds prevailed, the seasonal totals at the Lightship were respectively 46 and 60 per cent of the average totals for New York City. In years with more western winds, higher totals at the Lightship may be expected.

4. On the basis of the Lightship studies it may be estimated that in the course of an average ragweed season, New York City probably receives as much wind-borne ragweed pollen as it raises within its own city borders.

5. An elimination program designed to free the city of ragweed pollen will only be completely successful when ragweed plants are completely and permanently eradicated from wide areas in every direction from which winds may carry pollen into the city. In New York City's planning, ragweed areas to the west of the city are its greatest problem.

The authors are indebted to the following individuals for their assistance and cooperation: Mr. Julius Daniels, Dr. E. Walzer, Dr. E. Grossman, Dr. M. Albert, and Dr. S. Kaplan of The Jewish Hospital of Brooklyn; Mr. Logan, Commander Rohnke, and Lieutenant Mason, Aids to Navigation Division, United States Coast Guard, New York City; BM/1 E. Henfy, United States Coast Guard Station, Sandy Hook, N. J.; Miss M. Arnold, Mr. H. Sacher, Miss P. Wilcox, and Mrs. M. Kasden, Rockaway Beach Hospital, Rockaway Beach; Miss C. Beckwith and Mr. J. McGuire, United States Weather Bureau, Battery; Mr. R. McCoy, United States Weather Bureau, Central Park, Manhattan; Dr. A. Gordon, Dr. J. W. Bashe, Jr., Dr. I. Goldstein, and Dr. John Malone, Sea View Hospital, Staten Island; Mr. A. Smith, St. Peter's General Hospital, New Brunswick, N. J.; and the Laboratory Staff of the New Jersey State Hospital, Marlboro, N. J.

REFERENCES

1. Preliminary Report of The National Pollen Survey Committee of The American Academy of Allergy on Proposed Standardization of Pollen Counting Techniques (M. Walzer, Chairman), J. ALLERGY **17**: 178, 1946.
2. Report of The National Pollen Survey Committee of the American Academy of Allergy on a Conversion Factor for Gravity Slide Counts, J. ALLERGY **18**: 284, 1947.
3. Walzer, E. H., Sherman, J., Chait, R. A., and Walzer, M.: Survey of Ragweed Pollination in the New York Metropolitan District in 1946, New York State J. Med. **47**: 1979, 1947.
4. Walzer, E. H., Siegel, B. B., Chait, R. A., and Walzer, M.: Survey of Ragweed Pollination in the New York Metropolitan District in 1947, New York State J. Med. **48**: 2019, 1948.
5. Wiseman, R. D., Siegel, B. B., Glazer, I., Chait, R. A., and Walzer, M.: Surveys of Ragweed Pollination in the New York Metropolitan District in 1948 and 1949, New York State J. Med. **50**: 2552, 1950.
6. Durham, O. C.: Meteorologic Aspects of the National Ragweed Pollen Problem, J. ALLERGY **3**: 58, 1931.
7. Station Meteorological Summary, WBO, Trenton, N. J., August and September, 1949, U. S. Department of Commerce, Weather Bureau.
8. U. S. Department of Commerce, Weather Bureau, Monthly Meteorological Summary with Comparative Data, New York, N. Y. Months of August and September, 1949, City Office (Battery Place).
9. U. S. Department of Commerce, Weather Bureau, Station Meteorological Summary, U. S. Department of Commerce, Weather Bureau, New York, N. Y. (City Office), 17 Battery Place, August and September, 1950.
10. Sack, S. S.: How Far Can Wind-borne Pollen be Disseminated? J. ALLERGY **20**: 453, 1949.
11. Wiley, J. S.: Survey of Literature Relating to Atmospheric Pollens and Hay Fever. Federal Security Agency, Public Health Service. Environmental Health Center, Cincinnati, Ohio, January, 1950.

FRACTIONATION OF RAGWEED ANTIGENS BY THE USE OF ION EXCHANGE RESINS

RALPH BOOKMAN, M.D., AND HARRY WAX, PH.D., LOS ANGELES, CALIF.

THE heterogeneity of antigenic substances in the field of allergy is common knowledge. Efforts to separate and isolate individual components of clinically significant antigens have been made by many workers over the years. Such methods as dialysis, diffusion, adsorption, electrophoresis, and chromatography in addition to precipitation methods have been attempted.[1] Contradictory observations have resulted and no one has completely succeeded in isolating and characterizing any single essential antigen from mixtures of pollen extract. Much work remains to be done and the experiments to be described suggest a new avenue of approach to the problem. These experiments are of a preliminary nature and the authors wish to endow them with no more complexity or implication than the facts indicate.

The ion exchange resins have been shown to function with large molecules including proteins. For example, Hirs, Stein, and Moore[2] succeeded in recovering a purified preparation of the enzyme ribonuclease by chromatographic adsorption on a column of the cationic exchange resin Amberlite IRC-50. The activity of the enzyme was unaffected by the procedure and the authors suggested that the technique might apply to substances with molecular weights as high as 15,000 to 20,000. Tallan and Stein,[3] using the same resin, found that all of the lysozyme of egg white could be obtained from a single peak. Moore and Stein[4] used the resin Dowex-50 very effectively in the fractionation of mixtures of amino acids and achieved highly selective separations by this means. Sober, Kegeles, and Gutter[5] also used Dowex-50 and effected good resolution of the components of an egg white "albumin fraction" and of a mixture of bovine plasma albumin and carbon monoxide hemoglobin. They also showed the stability of highly purified egg albumin after passing through the resin. Such observations reveal the usefulness of ion exchange resins in fractionating proteins without significant modification of the resulting purified materials. Advantage was taken of these properties in the attempt to fractionate a pollen extract since the antigenic factors therein contained are also materials of high molecular weight and probably protein or at least polypeptide in character. The present investigation was performed in order to probe the potential of the ion exchange separation technique in the investigation of the heterogeneity of antigenic materials. For this purpose *Ambrosia trifida* was selected because most of the fractionating work in the past has been performed on extracts of this pollen.

From the George Piness, M.D., Allergy Group.

Presented at the Ninth Annual Meeting of The American Academy of Allergy, Boston, Mass., February, 1953.

Received for publication March 16, 1953.

MATERIALS AND METHODS

The ion exchange resins used were Dowex-50, a sulfonic acid type cation exchange resin; Dowex-2, a strong base anion exchange resin, and Amberlite IRC-50, a carboxylic acid type cation exchange resin. All three had been shown capable of adsorbing and resolving protein or related materials. The materials were used in the original state obtained from the manufacturer. The first experiment was an attempt to demonstrate that such adsorption and resolution took place with *Ambrosia trifida* and to assess such qualities in resins. The second experiment was a more carefully planned attempt to show the degree of fractionation possible with the materials used. Dowex-2, the anion exchange resin, was not used in the second experiment since it appeared that the cationic type resins effected more complete separation of nitrogenous material. All experiments were conducted at room temperature. Skin testing of fractions was performed by the usual intradermal technique on known reactors to *Ambrosia trifida*. Since this pollen is not a factor in Southern California we were able to cull only a few reactors from a large group of patients reviewed. Testing materials were coded to avoid prejudicial interpretation. Both original extracts and all fractions were diluted to achieve equal nitrogen content. All reactions were read at the end of twenty minutes and wheals were graded from zero to 4 plus.

METHODS

Experiment No. 1.—1. Three columns were prepared by inserting dry, weighed resin of 200 to 400 mesh particle size into 9 mm. glass tubes. The first two contained 4 Gm. of Dowex-50, hydrogen form, and 4 Gm. of Dowex-2, hydroxyl form, respectively. The third contained a mixture of 2 Gm. of each of the two resins.

2. An extract of *Ambrosia trifida* was prepared using 3 Gm. of defatted pollen per 100 c.c. of distilled water. This mixture was mechanically shaken for one hour and passed through a Seitz filter. The resulting solution had a nitrogen content of 0.27 mg. per cubic centimeter. Forty cubic centimeters of this extract was poured on the top of each resin column and allowed to seep through by gravity. The fluid which passed through each column was collected continuously and each succeeding 10 c.c. was regarded as a sample. The nitrogen content of these samples was determined by the micro-Kjeldahl method.

3. Distilled water was continuously added to the top of each column and the fluid which passed through was collected in successive 10 c.c. samples as before. This was continued until a sample was obtained from each column which showed a nitrogen content less than 0.02 mg. N./ml. Up to this point all nitrogenous material was regarded as having been unadsorbed. A sample from each column which showed the highest nitrogen content was reserved for skin testing.

4. Fifty cubic centimeters of a 1.0 molar solution of sodium bicarbonate was passed through each of the three columns by pouring above and collecting

below. Successive 10 c.c. lots were collected and nitrogen determinations made in each case. The material obtained from this procedure was regarded as having been adsorbed upon the resin columns and then eluted from them by the bicarbonate solution. Of this group of samples, the one from each column showing the highest nitrogen content was reserved for testing.

5. The skin testing group consisted of the three samples obtained in steps Nos. 2 and 3 and three samples obtained in step No. 4. In order to show that there was no material in the columns which might produce skin reactions, distilled water was passed through three columns of the resins described in step No. 1 and 1.0 molar sodium bicarbonate solution was passed through three similar but unused resin columns. Six samples were thus obtained for controls in addition to a simple saline control and the original pollen solution.

Experiment No. 2.—1. Two glass columns of resin were prepared. One contained Dowex-50 in its hydrogen form (4 Gm. dry resin) and the other Amberlite IRC-50 (7 Gm. dry resin). Each resin column measured 9 mm. by 150 mm. These resins were selected since in the hands of other workers they appeared to adsorb and resolve materials of high molecular weight.[2, 3, 5] The Dowex-50, in addition, appeared the more effective of the two resins used in the first experiment. The particle size of the resins was 200 to 400 mesh.

2. An extract of *Ambrosia trifida* was prepared as in Experiment No. 1, altering the proportions to 7 Gm. of defatted pollen per 100 c.c. of distilled water with a resulting nitrogen content of 0.69 mg. per cubic centimeter. It was felt that an increased concentration of the pollen solution might effect better separation.

3. Since there is evidence pointing to better equilibration between experimental material and the resin with a slow, standardized flow from the top to the bottom of the column, an effort was made to achieve this. In the first experiment the flow was rapid, averaging about 0.5 c.c. per minute. In this experiment the flow through the columns was at a rate of 3.0 c.c. per hour. This was accomplished by the use of a capillary tip at the bottom of the column and the application of positive or negative pressure at the top as changes in the rate of flow indicated. Compressed air and side-arm type suction were used. As solutions were passed through the column, successive 2 c.c. samples were collected continuously and both pH and nitrogen content of each sample was determined by the micro-Kjeldahl method.

4. Sixteen cubic centimeters of the pollen solution was passed through each column followed by distilled water until a sample of the effluent or fluid which had passed through the column had a nitrogen content less than 0.02 mg. N./ml.

5. Buffer solutions of 0.4 molar strength were prepared of sodium acetate, sodium phosphate, sodium bicarbonate, and sodium carbonate. This series represented buffers of increasing pH, the ranges being: sodium acetate pH 3.5-5.5, sodium phosphate pH 5.8-8, sodium bicarbonate pH 8.3-9.9, sodium carbonate pH 10-11.6. These were passed through the column in succession starting with sodium acetate. The change from one buffer to the next was

made when the pH of the effluent samples indicated the attainment of an equilibrium between buffer and sample or when it appeared that such an equilibrium could be attained only by the use of large amounts of buffer and requiring analysis of an unusually large number of samples.

6. A graph was prepared to illustrate the fractionation obtained in each resin column (Figs. 1 and 2). The abscissa represents the volume of fluid passing through the columns in terms of successive 2 c.c. samples so that each number represents a sample number rather than literal volume. The left-hand ordinate controls the unbroken line and indicates nitrogen content. The right-hand ordinate controls the broken line and indicates pH.

7. Skin test samples were selected from the peak of each rise in nitrogen content indicated on the graphs by circled numbers. The original pollen extract was used and the three controls consisted of the acetate, phosphate, and bicarbonate buffers. The carbonate buffer was too irritating for intradermal use. All samples and the ragweed control were adjusted to a pH range of 6.5 to 7.2. Buffer controls were not passed through columns or adjusted as to pH.

Experiment No. 1 Results.—The results of skin testing are shown in Table I. The column containing Dowex-2 adsorbed 56 per cent of the total nitrogen.

TABLE I. REACTIONS TO AMBROSIA TRIFIDA POLLEN FRACTIONS

	4 REACTION	3 REACTION	2 REACTION	NO REACTION
Dowex-2 unabsorbed	0	0	2	13
Dowex-2 H_2O control	0	0	4	11
Dowex-50 unabsorbed	5	6	3	1
Dowex-50 H_2O control	0	1	3	11
Dowex-2 and 50 unabsorbed	0	1	2	12
Dowex-2 and 50 H_2O control	0	0	1	14
Dowex-2 eluted absorbate	4	5	1	5
Dowex-2 bicarb. control	0	0	0	15
Dowex-50 eluted absorbate	4	6	1	4
Dowex-50 bicarb. control	0	0	4	11
Dowex-2 and 50 eluted absorbate	6	4	2	3
Dowex-2 and 50 bicarb. control	0	1	1	13
Unfractionated original extract	9	6	0	0
Saline control	0	0	1	14

The 44 per cent which passed through the column gave insignificant skin reactions. About 76 per cent of the adsorbed nitrogen was eluted by the sodium bicarbonate and tests performed with this fraction gave significantly positive skin reactions. The Dowex-50 column adsorbed 86 per cent of the total nitrogen yet the unadsorbed portion, representing only 14 per cent of the total nitrogen, gave significant skin reactions as did the fraction eluted from the column after adsorption. The latter represented 84 per cent of the amount adsorbed. The combined resins, Dowex-2 and 50, adsorbed 98 per cent of the total. While the unadsorbed fraction of 2 per cent gave reactions of little significance, the nitrogen content was so small that it could not be adjusted to a concentration

which might compare favorably with the other fractions tested. The material eluted from the column represented 83 per cent of the adsorbed nitrogen and gave significant skin reactions.

These results justified the conclusion that antigenic material was adsorbed by and then removed from columns of ion exchange resins. The character of the resin seemed to influence the amount which could be adsorbed and removed. It seemed likely that the antigenic material was not materially affected by the manipulations.

Experiment No. 2 Results.—Amberlite IRC-50 column: The first peak in the graph (Fig. 1) represents the unadsorbed nitrogenous substances. The remainder of the curve indicates the material which was adsorbed on the resin and then eluted by the buffer solutions. The presence of discrete peaks, following the first, demonstrates that fractionation had taken place. This occurred particularly in the acid range of pH.

TABLE II. REACTIONS TO AMBROSIA TRIFIDA POLLEN FRACTIONS

	4 REACTION	3 REACTION	2 REACTION	NO REACTION
Amberlite IRC-50				
Fraction No. 1	1	2	3	7
Fraction No. 2	0	0	0	13
Fraction No. 3	0	0	0	13
Fraction No. 4	0	2	2	9
Fraction No. 5	0	1	1	11
Dowex-50				
Fraction No. 1	3	5	4	1
Fraction No. 2	3	2	3	5
Fraction No. 3	2	3	4	4
Fraction No. 4	0	1	2	10
Fraction No. 5	0	1	5	7
Fraction No. 6	0	1	2	10
Fraction No. 7	0	2	4	7
Fraction No. 8	1	1	3	8
Fraction No. 9	0	2	4	7
Fraction No. 10	0	2	5	6
Fraction No. 11	0	2	2	9
Unfractionated original extract	4	4	5	0
Buffer controls				
Acetate	0	1	1	11
Phosphate	1	0	1	11
Bicarbonate	0	0	1	12

Five fractions were selected for testing. Four of these fractions represented discrete peaks in nitrogen content. The fifth fraction contained the only pigmented material which appeared during the experiment with this resin and appeared at a pH of about 8.5. Table II indicates that none of the fractions showed more than slight reactions on skin testing and that fractions 2 and 3 showed none at all. Since the total nitrogen content of all fractions obtained represented about 85 per cent of that of the original extract, the per cent remaining on the column at the end of the experiment may have contained the missing reactive substances. Another possible reason for the test results is that

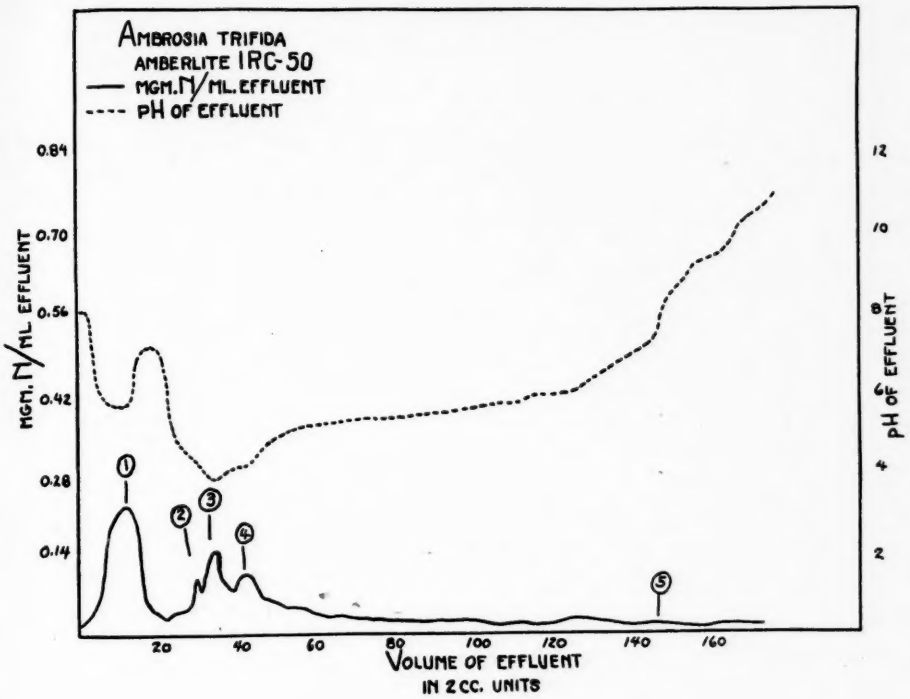

AMBROSIA TRIFIDA
AMBERLITE IRC-50
MGM. N/ML. EFFLUENT
pH OF EFFLUENT
MGM. N/ML EFFLUENT
pH OF EFFLUENT
VOLUME OF EFFLUENT
IN 2 CC. UNITS

Fig. 1.

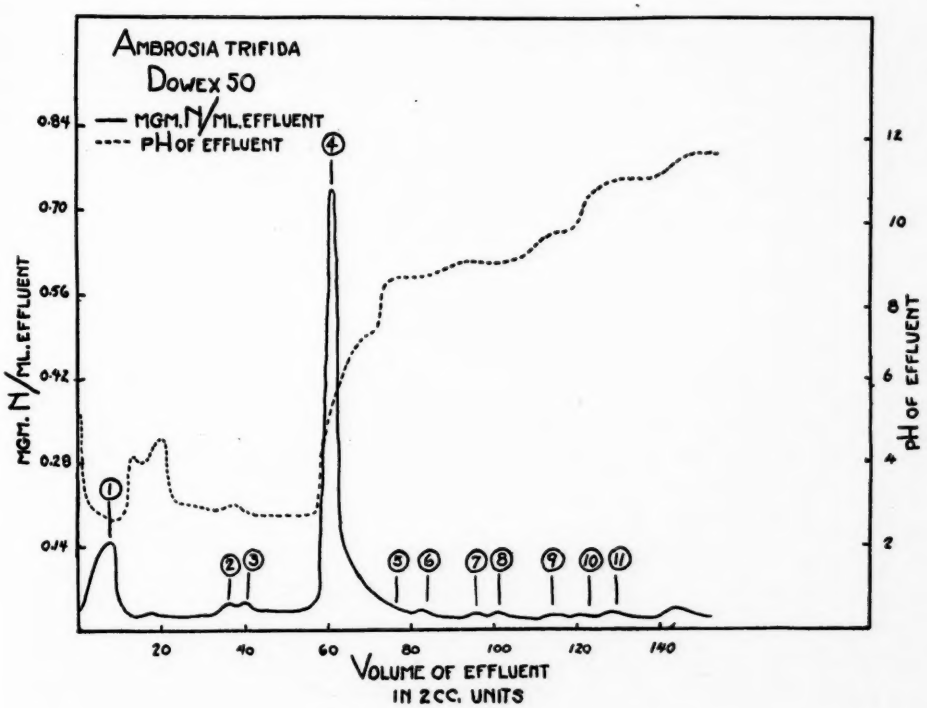

AMBROSIA TRIFIDA
DOWEX 50
MGM. N/ML. EFFLUENT
pH OF EFFLUENT
MGM. N/ML. EFFLUENT
pH OF EFFLUENT
VOLUME OF EFFLUENT
IN 2 CC. UNITS

Fig. 2.

the protein may have been altered as a result of the experimental procedure. Also, as will be emphasized later, the high nitrogen contents of the peak fractions may not necessarily represent high contents of antigenic material.

Dowex-50 column: Here again the first peak on the graph (Fig. 2) represents the unadsorbed nitrogenous material and the peaks which follow indicate the nitrogen-containing substances eluted from the column after adsorption. The sharp peak, 4, which represents about 50 per cent of the total nitrogen content of the effluent, is particularly prominent. Fractions 5 through 11, which follow the major nitrogen peak, represent the appearance of pigments, each of which was associated with a slight but definite rise in nitrogen content. Each pigmented effluent was separated from the others by colorless fractions. Fraction 5, while it seems to be on the descending limb of the major peak, represents the appearance of a pigmented effluent. All of the pigments appeared in the alkaline range of pH.

Eleven fractions from this column were selected for testing. Four represented definite peaks in nitrogen content and seven were pigmented. Table II indicates that all fractions retained a certain degree of skin reactivity. Fraction 1, the unadsorbed nitrogen, gave the strongest reactions. Fractions 2 and 3, although of comparatively low nitrogen contents, were also quite reactive. Fraction 4, despite its magnitude, showed such weak reactions that its antigenicity may be questioned. The pigmented fractions 5 through 9 showed enough skin reactivity, despite their low nitrogen content, to lead to the conclusion that they probably contained antigenic material.

Fractionation of nitrogenous material unquestionably took place in both columns. The pattern of this fractionation was quite different for each resin despite similar procedures. Obviously, the nature of the fractionation is profoundly influenced by the type of resin employed.

Skin reactions differed between fractions from the two resin columns. Both unadsorbed fractions showed good skin responses but neither these nor any of the fractions obtained should be construed as being homogenous. The complete dissociation between nitrogen content and skin reactions was strikingly illustrated by the results on the Dowex-50 column. The major component of the effluent failed to give satisfactory reactions whereas the two minor peaks which preceded it gave satisfactory skin responses. While alteration of the protein content of the large fraction 4 is conceivable, the activity of the previous two eluted fractions does not support this. Many facts have been presented in the past to show how inconsistent it is to relate antigen strength to nitrogen content. The results here further disprove this misleading but all too common practice.

The pigmented fractions showed sufficient reaction on skin testing to suggest antigenicity. This cannot necessarily be attributed to the pigments since each fraction had a significant nitrogen content.

SUMMARY AND CONCLUSIONS

1. *Ambrosia trifida* extract was passed through columns of various ion exchange resins.

2. Fractionation of the original nitrogenous material was shown to occur by this method.

3. Skin testing of known reactors to the original extract suggested that certain fractions were antigenically active while other fractions showed little or no such activity.

4. The nitrogen content of fractions and their antigenicity appear to be unrelated, suggesting that this is also true of the whole extract.

5. The methods and results suggest a new approach to the isolation of individual components of antigenic material.

REFERENCES

1. Friedmann, R. A.: Chemical and Immunological Properties of Timothy Grass Pollen Extracts and Problems of Standardization, Quart. Rev. Allergy **6**: 290, 1952.
2. Hirs, C. H. W., Stein, W. H., and Moore, S.: Chromatography of Proteins. Ribonuclease, J. Am. Chem. Soc. **73**: 1893, 1951.
3. Tallan, H. H., and Stein, W. H.: Studies on Lysozyme, J. Am. Chem. Soc. **73**: 2976, 1951.
4. Moore, S., and Stein, W. H.: Chromatography of Amino Acids on Sulfonated Polystyrene Resins, J. Biol. Chem. **192**: 663, 1951.
5. Sober, H. A., Kegeles, G., and Gutter, F. J.: Chromatography of Proteins. Frontal Analysis on a Cation Exchange Resin, J. Am. Chem. Soc. **74**: 2735, 1952.

LATENT ATOPY AND THE INCIDENCE OF THE ATOPIC STATE

SHEPPARD SIEGAL, M.D., AND THOMAS SEIDEMAN, M.D., NEW YORK, N. Y.

THE purpose of the present investigation is to focus attention upon the state of latent or subclinical atopy and to determine more precisely the true incidence of atopy. Cooke[1] has observed that "skin tests with a few of the more important allergens, if definitely positive and confirmed, are indicative of the allergic state." In the present study an effort is made to reveal the incidence of the latent phase of atopy, utilizing as an indicator the response on intracutaneous testing with pollen and dander extracts. From the observations here reported it appears probable that the constitutionally allergic person is not, as commonly stated, one in ten in the general population,[2-4] but rather one in five.

MATERIAL AND METHODS

Two hundred twenty-seven patients admitted to the general surgical wards of the Mt. Sinai Hospital, New York, comprise the case material of this study. The patients selected for study were those with conditions not in any sense considered to have any relationship to atopy. Otherwise they were unselected consecutive admissions.

In this patient group were 98 cases of neoplasm, chiefly fibromyoma uteri, gastrointestinal carcinoma, and benign prostatic hypertrophy; 34 cases with acute or chronic infection, chiefly pelvic inflammatory disease, acute appendicitis, and superficial cellulitis; 33 cases with defects such as hernia, cystocele, rectocele, and uterine prolapse, or hydrocele; 24 instances of gall bladder and urinary tract calculi; and 28 others with hemorrhoids, rectal fistulas, and menometrorrhagia; also 10 instances of trauma, chiefly fractures. Patients with a past or present history of peptic ulcer, ulcerative colitis, regional enteritis, or diabetes mellitus were excluded from this study.

Of the 227 persons 136 were female and 91 were male, and they ranged in age from 11 to 82 years, predominantly between 30 and 70. Included were native American, Italian, Irish, Negro, Puerto Rican, and Jewish subjects.

Each patient was questioned as to the occurrence of symptoms of hay fever, vasomotor rhinitis, bronchial asthma, or of atopic eczema. Clinically manifest atopy was considered present if such symptoms had occurred at any time, whether or not they were currently active. In this study latent atopy is conceived as being completely subclinical, the patient not having any symptoms of the conditions mentioned at any time.

The term atopy has been employed with somewhat varying connotations. As defined by Coca,[5] it referred to "certain clinical forms of human hypersensitiveness that do not occur, so far as is known, in the lower animals, and which are subject to hereditary influence. In this category have been included

From the Adult Allergy Clinic, The Mount Sinai Hospital.
Received for publication May 2, 1953.

thus far only asthma and hay fever, but it is generally thought that eczema and certain forms of drug and food idiosyncrasy will eventually be placed with these."

As it is now known that hay fever due to pollen allergy may occur in animals, the above definition is in part no longer valid. However, the essential point remains that atopy includes those clinical forms of allergy subject to hereditary influence. Atopic dermatitis has been included by most observers in the atopic category. Others have emphasized the presence of immediate wheal type skin reactions and the demonstration of circulating reagin. It has been shown, however, that bronchial asthma with negative skin tests is as subject to hereditary influence as when positive skin tests are present.[6] It is probable that this is likewise true for vasomotor rhinitis, and nasal polyps are generally regarded as a manifestation of atopy.

Each subject was tested intracutaneously with extracts of the four major pollen groups, a mixture of long and short ragweed, mixed timothy and orchard grass, English plantain, and a mixed extract of trees, employing two concentrations, 100 and 5,000 protein nitrogen units per milliliter. Dog, cat, and horse dander extracts were also used in two concentrations, 0.001 and 0.01 mg. of total nitrogen per milliliter. Although many patients were tested with other extracts as well, the responses to pollen and dander extracts alone were considered in determining whether an immunologic reaction indicative of atopy was present.

The tests were carried out in the standard manner of allergy testing, using an injection of approximately 0.02 ml. volume. Reactions were read conservatively, borderline or plus-minus responses not being included in the positive category. A control test with buffered saline was made for each subject at each session of testing. Of 19 subjects who gave positive skin reactions in the absence of all allergic symptoms, 12 were retested to determine the validity of the initial findings. Five of these subjects with persistent positive skin reactions, but who had no symptoms of allergy, were tested by the passive transfer method.

Latent atopy was considered present if, despite the absence of atopic manifestations, either a single 4 plus reaction or two or more 2-3 plus reactions were obtained, and could be confirmed by retest.

OBSERVATIONS

1. Clinically overt atopy, or the occurrence of the previously designated allergic syndromes, was found in 32 of the 227 subjects investigated. This represents an incidence of 14 per cent. Included in this group were 13 patients with bronchial asthma, 11 with ragweed hay fever, 2 cases of allergic rhinitis due to specific allergens other than pollen, one case of repeated nasal polyps with positive skin tests, one of vasomotor rhinitis with positive skin tests, and four instances of vasomotor rhinitis with skin tests which were negative according to the criteria established for the diagnosis of latent atopy.

2. Nineteen subjects gave positive skin reactions of a degree considered indicative of atopy despite the absence of allergic symptoms; 12 of these were

retested, and 10 again gave positive reactions of similar degree and were therefore considered as falling in the category of latent atopy. Seven more patients were positive on test but were not available for retesting. On the basis of those retested, the conclusion appears warranted that five of these would have proved positive on retest. The total incidence of latent atopy is thus calculated to be 15 subjects or 6.6 per cent (Table I).

TABLE I. FIFTEEN PATIENTS WITH LATENT OR SUBCLINICAL ATOPY

PATIENT, AGE, SEX	MEDICAL DIAGNOSIS	INITIAL INTRADERMAL TEST*	SECOND INTRADERMAL TEST	PASSIVE TRANSFER TEST
1. D. F. 44 F.	Fibromyoma uteri	Ragweed 100 PNU 4+ Grass 5,000 PNU 3+ Dog, cat ep. 0.001 N 2+	Ragweed 100 PNU 4+ Grass 5,000 PNU 4+ 3+ Cat ep. 0.001 N 2+	Ragweed 100 PNU 1+ 5,000 Others, neg.
2. P. G. 11 M.	Acute appendicitis	Horse ep. 0.001 4+ Ragweed 5,000 2+ Grass, trees 5,000 2+	Horse ep. 0.001 4+ Ragweed, grass, trees 5,000 2+	Negative
3. L. M. 25 F.	Metrorrhagia	Grass 100 2+ 5,000 4+ Ragweed 5,000 3+	Grass 100 3+ 5,000 4+	Negative
4. A. M. 36 F.	Metrorrhagia	Ragweed 5,000 4+	Ragweed 5,000 4+	Negative
5. L. L. 38 M.	Inguinal hernia	Ragweed 100, 5,000 2+ Trees 5,000 3+ Grass 5,000 2+	Ragweed 5,000 4+ Trees 5,000 3+	Negative
6. Y. R. 22 F.	Bartholin cyst	Ragweed 100 2+ 5,000 4+ Trees 5,000 2+	Ragweed 100 4+ 5,000 4+	—
7. E. M. 52 F.	Carcinoma of sigmoid	Ragweed 5,000 2+ Dog ep. 0.001 2+ Cat ep. 0.01 2+	Ragweed 5,000 2+ Dog, cat ep. 2+	—
8. A. J. 34 M.	Therapeutic abortion Pulmonary embolism	Grass 5,000 4+ Ragweed 100 2+ 5,000 3+	Ragweed 5,000 4+ Grass 5,000 4+	—
9. G. S. 20 M.	Fracture of carpal navicular	Grass 5,000 2+ Ragweed 5,000 2+	Ragweed 5,000 2+ Grass 5,000 2+	—
10. H. W. 65 F.	Carcinoma of breast	Ragweed 5,000 2+ Grass 5,000 2+	Ragweed 5,000 2+ Grass 5,000 2+	—
11. H. B. 59 M.	Carcinoma of bladder	Grass 100 2+ 5,000 4+ Ragweed 100 2+ Eng. plantain 100 2+	—	—
12. E. H. 60 M.	Carcinoma of stomach	Ragweed 100 1+ 5,000 4+	—	—
13. S. L. 50 F.	Putrid lung abscess	Ragweed 5,000 4+	—	—
14. E. D. 44 M.	Fracture of mandible	Ragweed 100 4+ Grass 100 2+	—	—
15. K. Y. 30 M.	Inguinal hernia	Ragweed 5,000 3+ Eng. plantain 5,000 3+ Dog ep. 0.01 2+ Dog ep. 0.001 1+	—	—

*Extracts employed for testing are described in the section on materials and methods.

3. Atopy, both in latent and manifest phases, therefore appeared to be present in 47 of the 227 subjects, or 20.7 per cent.

4. Passive transfer tests carried out with the serum of five subjects with latent atopy, who were positive on direct skin test and confirmed by retest,

were positive in one case and negative in four cases. To make more certain that our technique and recipients were adequate for passive transfer, simultaneous testing was carried out with the serum of a ragweed hay fever patient with strongly positive skin tests. This showed a strong positive passive transfer reaction (Table I).

DISCUSSION

Recently, Miller[7] used intracutaneous testing to determine the incidence of atopy among 216 medical students. However, his results are not comparable with ours because he accepted, as indicative, reactions to a greater variety of inhalants, and apparently did not retest his subjects. Also he included within the latent group those with a positive past history of allergic symptoms, although currently asymptomatic. He found a surprisingly high total incidence of atopy of 60 per cent, of which 47 per cent were in the clinically overt category. Our finding of a 14.1 per cent incidence of atopy with clinical manifestations is more in accord with previous estimates.[1-3]

While the concept of a latent phase of allergy is widely accepted, the present study attempts a quantitative estimate of its occurrence. Our findings suggest that among the 20 per cent of the general population affected by atopy, two-thirds are in the clinically manifest phase and one-third in the latent or subclinical phase.

Of interest are the negative passive transfer reactions in four of five subjects with latent atopy. Each of these patients with negative passive transfer tests was four plus positive on direct skin test. These findings suggest the possibility that atopy in its latent phase may not usually be characterized by the presence of circulating reagin in sufficient titer to permit positive passive transfer. This would be in contrast with the clinically overt phase of atopy in which positive reactions on direct skin test can usually be confirmed by a positive passive transfer test. However, further study would be necessary to clarify this phase of the problem.

SUMMARY

1. Two hundred twenty-seven persons admitted to the surgical wards of a general hospital for conditions not known to have any relation to atopy were tested intracutaneously with pollen and dander extracts, and interrogated as to the occurrence of clinical manifestations of atopy.

2. The latent, or subclinical, phase of atopy as indicated by reactions to intracutaneous testing in the absence of past or present allergic symptoms, was observed in 15 subjects, or 6.6 per cent. Atopy in its clinically manifest phase was found in 32 subjects, or 14.1 per cent, making a total incidence of 47 or 20.7 per cent.

3. Accordingly from this study it would appear that the total incidence of atopy in the general population is about 20 per cent, two-thirds being in the clinical phase and one-third in the latent phase.

4. Five subjects with latent atopy were tested by the passive transfer method. In only one case was this positive, in four others negative. It is sug-

gested that in the latent phase of atopy circulating reagins may not usually be present in sufficient titer to permit a positive passive transfer reaction despite the presence of repeated strong reactions on direct skin testing.

We gratefully acknowledge our debt to Mrs. Irving Bodenheimer for her cooperation and competence in carrying out much of the intracutaneous testing.

REFERENCES

1. Cooke, R. A., and Vanderveer, A., Jr.: Human Sensitization, J. Immunol. **1:** 201, 1916.
2. Jiminez, B.: A Survey of Sensitization in Students of the University of Michigan, J. Michigan M. Soc. **33:** 310, 1934.
3. Pipes, D.: The Incidence of Major and Minor Allergy in the Deep South, South. M. J. **30:** 1012, 1937.
4. Cooke, R. A.: Allergy in Theory and Practice, Philadelphia, 1947, W. B. Saunders Company, p. 144.
5. Coca, A. F., in Coca, A. F., Walzer, W., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, 1931, Charles C Thomas, p. 38.
6. Cooke, R. A.: Infective Asthma: Indication of Its Allergic Nature, Am. J. M. Sc. **183:** 309, 1932.
7. Miller, H.: A Study of Clinical and Immunologic (Reaginic) Allergy in a Group of Medical Students, J. ALLERGY **22:** 475, 1951.

ATOPY AND DIABETES MELLITUS

SHEPPARD SIEGAL, M.D., AND JOSEPH HERZSTEIN, M.D., NEW YORK, N. Y.

ATOPY and diabetes are two of the most common disease states in which a definite hereditary constitutional factor appears to be operative. For this reason alone it seemed worth while to study the incidence of atopic symptoms and stigmata among diabetic patients. The occasional occurrence of specific allergy to insulin among diabetic individuals,[1] and at times the appearance of a state of insulin refractoriness accompanying or following periods of insulin allergy provided a further stimulus for this investigation. The fact that a diabetic patient might be precipitated into a state of severe resistance to the hormonal activity of insulin by means of an immunologic mechanism[2, 3, 6] suggested the possibility that some phase of diabetes might likewise be mediated through an immunologic or allergic disturbance. Such a concept of the pathogenesis of diabetes suggested itself especially for the more severe cases of diabetes in which the patients require large daily doses of insulin for adequate control. The present study deals therefore with the incidence of clinically manifest and latent atopy in a group of 40 diabetic patients who required large amounts of insulin daily, and in a second group of 227 nondiabetic patients used as a control.

MATERIAL AND METHODS

Forty diabetics with daily insulin requirements of 50 to 110 units were questioned carefully as to symptoms of hay fever, vasomotor rhinitis, bronchial asthma, and eczema. Patients who had such manifestations at any time were considered to have clinically overt atopy. Latent or subclinical atopy was determined on the basis of response to intracutaneous tests with pollen and dander extracts. The tests were carried out as in routine allergy testing by the intracutaneous injection of approximately 0.02 ml. We tested with mixed ragweed, mixed grass, English plantain, and mixed tree pollen extracts in two concentrations, 100 and 5,000 protein nitrogen units per milliliter, and with dog, cat, and horse epidermis extracts in concentrations of 0.001 N and 0.01 N per milliliter. Latent atopy, was considered present if, despite the absence of atopic manifestations, either a single 4 plus reaction or two or more 2-3 plus reactions were obtained, and could be confirmed by retest.

The diabetic patients ranged in age from 19 to 73 years, with the largest number in the sixth decade. There were 24 female and 16 male patients. The onset of diabetes in most instances was in the fifth decade, although in ten patients it began before the age of 30. In the group were patients of American, Irish, Italian, and Puerto Rican origin. The control group consisted of nondiabetic patients on the surgical wards of the hospital who were admitted for

From the Adult Allergy and Diabetes Clinics, The Mount Sinai Hospital.
Received for publication May 2, 1953.

conditions not known to be related to atopy. Their ages ranged from 11 to 82 years; most were over 40 years old. There were 136 female and 91 male patients. The complete data regarding the control group appear elsewhere.[5]

OBSERVATIONS

Clinically manifest atopy, comprising a history of hay fever, definite vasomotor rhinitis, bronchial asthma or atopic eczema, was found in 6 diabetic subjects, an incidence of 15 per cent. In this clinically atopic group were 3 patients with bronchial asthma and 2 with vasomotor rhinitis, showing positive skin tests. The sixth patient had a definite history of gastrointestinal reaction to scallops, and vasomotor rhinitis with negative skin tests.

Three other diabetic patients who had no allergic symptoms gave positive skin reactions to two or more extracts. One of these patients had a 4 plus reaction to ragweed and 2 plus reactions to grass, dog, and cat epidermal extracts. A second patient showed 2 plus reactions to both ragweed and English plantain extracts, while a third gave 2 plus reactions to all the pollen and dander extracts used in the tests. Control tests were negative in each of these patients. Retests were not carried out. On the basis of our findings in the control series, at least two of these three cases would doubtless be confirmed and may be considered true instances of latent atopy. Altogether 8 of the 40 diabetic patients presented clinical or latent atopy, amounting to an incidence of 20 per cent.

In the control group of 227 nondiabetic individuals there were 32 instances of clinical atopy and 15 of latent atopy, making a total of 47, a percentage incidence of 20.7 per cent.[5] This was almost identical with the percentage found in this group of severe diabetic patients.

COMMENT

Kern[4] found the incidence of clinically manifest atopy among 300 diabetic patients of varying degree of severity to be 20.3 per cent. This is but slightly higher than the incidence of 15 per cent of clinically manifest atopy in our selected smaller group with severe diabetes. It appears that the incidence of atopy either in mild or in severe diabetic patients shows no indication of a hereditary cross relationship between the two states. The hypothesis that the severe form of diabetes might have some obscure immunologic pathogenesis, related to that which on occasion is observed in insulin resistance,[2, 6] is not borne out by the indirect observations made in this study. If there is such a mechanism, it does not appear to be related to the atopic state.

SUMMARY

Among 40 diabetic patients, whose insulin requirement was from 50 to 110 units a day, 8 individuals were found to have either clinically manifest or latent atopy, an incidence of 20 per cent. There were 6 patients with the clinical phase of atopy and 2 with the latent phase of atopy.

An almost identical incidence of atopy, 20.7 per cent, was found in parallel observations in a nondiabetic control group of 227 patients, 47 of whom had clinical or latent atopy.

These observations would indicate that there exists no special relationship between the two hereditary states of atopy and diabetes mellitus. Patients with severe diabetes have not been shown to have any unusual predisposition to atopy. It appears unlikely that diabetes of the severer type is based on any immunologic mechanism such as seems to occur in rare instances of insulin resistance and allergy.

REFERENCES

1. Herzstein, J., and Pollack, H.: Insulin Allergy, J. Mt. Sinai Hosp. **6**: 3, 1939.
2. Lowell, F. C.: Immunologic Studies in Insulin Resistance, J. Clin. Invest. **23**: 225, 233, 1944.
3. Loveless, M. H.: Co-existence of Two Antibodies for Crystalline Insulin in Human Serum, Federation Proc. **5**: 250, 1946.
4. Kern, R. A.: Studies in Heredity in Allergy and in Diabetes, Tr. Assoc. Am. Phys. **49**: 23, 1934.
5. Siegal, S., and Seideman, T.: Latent Atopy and the Incidence of the Atopic State, J. ALLERGY **25**: 20, 1953.
6. Davidson, J. K., III, and Eddleman, E. E., Jr.: Insulin Resistance, Arch. Int. Med. **86**: 727, 1950.

CIRCULATORY EFFECTS OF ADRENOCORTICAL LACK AND EXCESS OBSERVED IN THE HAMSTER CHEEK POUCH*

MAURICE H. SHULMAN, M.D., LELAND C. WYMAN, PH.D., AND GEORGE P. FULTON, PH.D., BOSTON, MASS.

THE efficacy of the corticosteroids in the allergic state is well established. The mechanism of action of the steroids, however, is not clear. This study was undertaken to visualize by direct microscopy the effect of the adrenocortical hormones on the smooth muscle and the endothelium of the peripheral vascular system. For this purpose, we have used the everted cheek pouch of the hamster transillumined for observation and motion picture recording of significant circulatory changes. The vascular effects of adrenal insufficiency and experimental hypercorticalism with cortisone or with desoxycorticosterone acetate (DCA) were studied.

CIRCULATORY FINDINGS AFTER ADRENALECTOMY

Bilateral adrenalectomies were made on 60 male hamsters ranging from 80 to 100 grams in body weight and varying from 8 to 10 weeks in age. As shown by Snyder and Wyman,[1] adrenalectomized hamsters live five to seven days without sodium chloride in the drinking water. Daily microscopic observations were made on the state of the small blood vessels and the condition of blood flow in the everted cheek pouch. The cheek pouch was prepared for transillumination under Nembutal anesthesia, according to the method of Lutz, Fulton, and Akers.[2]

No significant variations from the normal appearance of the small blood vessels were seen by microscopy during the initial postoperative period. A fairly rapid blood flow was maintained and the muscular arterioles remained narrow. Stasis and erythrocytic extravasations (petechiae) were absent.

Within twenty-four hours of death, the blood flow became slow and sluggish in the cheek pouch. Stasis developed in the venules and capillaries. The decreased rate of blood flow is probably due to increased vascular permeability, bradycardia, and other cardiac disturbances characteristic of hyperpotassemia. Thus, the heart rate decreased from a normal range of 350 to 450 per minute prior to adrenalectomy, to values approaching 150 near death. Furthermore, the electrocardiograms were indicative of potassium poisoning.

Following adrenalectomy, the arterioles of the cheek pouch became narrower as death approached. Rhythmic contractions and relaxations of the arteriolar walls (vasomotion) occurred at times after adrenalectomy but

From the Department of Biology, Boston University.

Received for publication July 20, 1953.

*Supported, in part, by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service.

rarely in normal hamsters. This is contrary to the reported loss of vascular muscle tonus in the mesoappendix of the adrenalectomized rat (Chambers and Zweifach[3]). The sensitivity of the vascular smooth muscle was tested in two ways: first, by determination of the threshold voltage required to produce constriction at the tip of a microelectrode[4, 5] applied by micromanipulation to the wall of an arteriole; and, second, by determination of the threshold concentration of nor-epinephrine (Levophed)* required for vasoconstriction during topical application from a micropipette. The results were an increased sensitivity to electrical stimulation (threshold of 3 volt single shock of 10 milliseconds in normal hamster as compared with 1.9 volt single shock after adrenalectomy), but a decreased sensitivity to nor-epinephrine (threshold range of 1:1,500,000 to 1:2,500,000 in normal hamster as compared with 1:900,000 to 1:1,000,000 after adrenalectomy).

In the absence of visible alterations in the endothelium, the susceptibility of the blood vessels of the cheek pouch to petechial formation was determined by use of a suction cup (1.4 cm. in diameter) and a negative pressure apparatus modified from the method described by Shulman and co-workers.[6] Spontaneous petechiae are seldom found in the cheek pouch of the normal hamster, and 30 cm. Hg negative pressure is required to produce from 1 to 5 petechiae. None is produced at 20 cm. Hg. During the first several days after adrenalectomy, the vascular "fragility" was greater as shown by 15 to 40 petechiae at 30 cm. Hg. When the insufficiency became severe at 5 to 7 days, the blood vessels were resistant to petechial formation, coincident with the progressive vasoconstriction. The site of formation of petechiae was discovered to be consistently the junction of small venules with other venules.[7] Petechiae were not formed on the capillaries, and consequently the term "capillary fragility" is not appropriate.

CIRCULATORY EFFECTS OF CORTISONE ACETATE

Normal hamsters with intact adrenal glands were given daily subcutaneous injections of Cortone (cortisone acetate, Merck†) in 3 groups: 10 hamsters received 5 mg. for twenty-one days; 10 received 10 mg. for twenty-one days or until death; and 4 received 15 mg. These doses are the approximate equivalents of 50, 100, and 150 mg. per kilogram daily. The hamsters treated with 5 or 10 mg. daily died in fourteen to thirty days, and those treated with 15 mg. died in twelve to twenty-one days.

The small blood vessels were examined daily and vascular "fragility" was determined by the negative pressure method. The threshold of the vascular smooth muscle to vasoconstrictor substances was tested by topical application of nor-epinephrine (Levophed), and the threshold to electrical stimulation by application of a microelectrode to the vessel wall.

Constriction predominated in the arterioles (Fig. 1, *A* and *B*) during treatment with cortisone, and the precapillary sphincters were relatively narrow. In 12 hamsters the arterioles were constricted by concentrations of nor-epinephrine varying from 1:900,000 to 1:1,500,000, indicating a decreased

*Kindly supplied by Winthrop-Stearns, Inc.
†Kindly supplied by Dr. Elmer Alpert, Merck and Company, Inc.

sensitivity in comparison with normal hamsters (1:1,500,000 to 1:2,500,000). The sensitivity of the vascular smooth muscle to electrical stimulation was also less than that of the normal as well as the adrenalectomized hamster. Furthermore, the blood vessels during treatment were resistant to petechial formation in response to the negative pressure test. A negative pressure of 30 cm. Hg produced relatively few petechiae after 13 days of 5 mg. cortisone and none after fifteen to twenty-two days of 5, 10, or 15 mg. daily. The vasoconstricting effect of cortisone may account for the increased resistance to petechial formation.

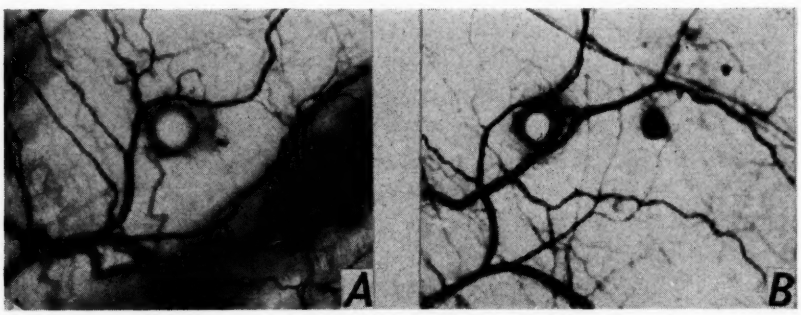


Fig. 1.—Comparison of vessel size in hamster cheek pouch before and after cortisone treatment (10 mg. daily). (×7.) *A*, Before instituting cortisone treatment. Inert glass bead used for vessel identification. *B*, Identical vessels showing vasoconstriction after twelve days of cortisone treatment.

The characteristics of the blood flow were modified significantly near death from cortisone. The endothelium of the venules became lined with sticking leukocytes forming an immobilized pavement, concurrent with a leukocytosis determined by white cell counts from blood obtained by cardiac puncture (8,000 to 52,000 per cubic millimeter). Furthermore, the erythrocytes often formed loose aggregates resulting in granular blood flow or sometimes "chunky" flow like that reported in lethally irradiated hamsters near death (Fulton, Lutz, Joftes, and Maynard[8]). This type of flow resembled "sludged blood" described by Knisely and co-workers[9] in the mesenteric blood vessels of monkeys during infection with *Plasmodium knowlesi* and subsequently reported by the same investigators in the conjunctival vessels of patients with a variety of diseases.[10] The concept of "sludged blood" implies that erythrocytic masses may block small vessels with serious consequences. The status of this concept and the role of other formed elements (especially platelets) in intravascular agglutination have been reviewed critically by Lutz.[11] The term "sludged blood" is probably not appropriate in the present investigation because the aggregates resolved into discrete erythrocytes at capillary origins without occluding the vessels.

Although the normal hamster is highly resistant to infection in the cheek pouch, treatment with cortisone was followed by local infections in more than 50 per cent of the animals, especially at points of lesion (pinholes from everting the pouch). The physiologic rationale for the contraindication of cortisone in the presence of acute infection has not been adequately defined. Shwartzman, Schneierson, and Soffer[12] reported that cortisone and ACTH suppressed the

local tissue reactions involved in the inflammatory response. Moon and Tershakovec[13] described a decrease in the diapedesis and edema associated with thermal burns in cortisone-treated guinea pigs, and explained the effects on the basis of an increased "capillary" resistance. Menkin[14] reported that cortisone and ACTH inhibited the increase in capillary permeability which normally accompanies inflammation. Ebert,[15] using the rabbit ear chamber technique, found that cortisone reduced the inflammatory response to tuberculous infection. He observed better maintenance of vascular tone, reduced damage to vascular endothelium, and decreased diapedesis after cortisone. Ashton and Cook[16] reported that cortisone produced vasoconstriction of the newly formed vessels in transparent chambers in the rabbit ear. The vasoconstrictor effect of cortisone, with accompanying suppression of the compensatory inflammatory reaction, might well be the explanation for the tendency for infection to occur.

CIRCULATORY FINDINGS DURING DCA TREATMENT

Normal hamsters with intact adrenals were injected subcutaneously with 1 mg. of desoxycorticosterone acetate (Percorten Microcrystalline*) daily, and given 1 per cent sodium chloride in their drinking water, and the vascular effects were studied in the cheek pouch at intervals until death from steroid treatment within ten to twenty days. Also, small DCA pellets were implanted in one cheek pouch and observations were made in both pouches.

The blood vessels remained relatively normal in appearance for seven to ten days during treatment. Subsequently, a marked weight loss occurred and some arterioles appeared constricted, especially in the terminal stage. Nevertheless, the vasoconstriction obtained with DCA was much less extensive than that produced by cortisone. The nor-epinephrine and electrical stimulation tests for smooth muscle sensitivity showed no significant deviations from the normal ranges. An increased susceptibility to petechial formation resulting from negative pressure (from 6 to 10 petechiae at 20 cm. Hg) persisted throughout the entire period of treatment with DCA, DCA plus salt, and DCA in pellet form. Infections in the cheek pouch were lacking during treatment with DCA.

In the cheek pouches containing implanted pellets, arterioles were frequently constricted for short lengths, producing a sausage-like appearance. Furthermore, individual skeletal muscle fibers in the pouch twitched intermittently.

SUMMARY

The circulation in the everted, transillumined cheek pouch of adrenalectomized hamsters and the microscopic appearance of the small blood vessels remained essentially normal until twenty-four hours before death at five to seven days. The rate of blood flow then diminished and stasis developed. In terminal stages of adrenal insufficiency, the arterioles were frequently constricted. The threshold of the vascular smooth muscle to direct electrical stimulation with a microelectrode remained low as compared with normal

*Kindly supplied by Dr. Robert Gaunt, Ciba Pharmaceutical Products, Inc.

values, but the threshold to topically applied nor-epinephrine increased slightly. An increased susceptibility to petechial formation from negative pressure occurred at one to three days after adrenalectomy, but an increased resistance developed terminally, paralleling the onset of vasoconstriction.

Cortisone acetate (5 mg. daily doses) produced arterial vasoconstriction in the cheek pouch of normal hamsters with intact adrenal glands, persisting from an early period until death at fourteen to thirty days. The threshold of the vascular smooth muscle to the microelectrode test and also to the nor-epinephrine test was elevated. The persistent vasoconstriction may explain clinical findings such as the tendency for infection to occur. Furthermore, vasoconstriction may also explain the increased resistance to petechial formation induced by negative pressure. A significant finding may be the sticking of leukocytes to the endothelial lining of venules and the concomitant leukocytosis during prolonged cortisone treatment.

DCA (1 mg. daily plus 1 per cent saline) produced no significant changes in the microscopic appearance of cheek pouch blood vessels until the period of severe weight loss prior to death. An increased vascular fragility persisted during DCA administration as indicated by the negative pressure test. Although vascular spasm was observed occasionally, DCA did not produce vasoconstriction comparable to that caused by cortisone.

REFERENCES

1. Snyder, J. G., and Wyman, L. C.: Gonadal Influences on Survival After Adenalectomy in the Golden Hamster, Endocrinology **49**: 205, 1951.
2. Lutz, B. R., Fulton, G. P., and Akers, R. P.: White Thromboembolism in the Hamster Cheek Pouch After Trauma, Infection and Neoplasia, Circulation **3**: 339, 1951.
3. Chambers, R., and Zweifach, B. W.: Intercellular Cement and Capillary Permeability, Physiol. Rev. **27**: 436, 1947.
4. Fulton, G. P.: A Silver-Glass Microelectrode for Use in a Micromanipulator, Proc. Soc. Exper. Biol. & Med. **48**: 427, 1951.
5. Fulton, G. P., Akers, R. P., and Lutz, B. R.: White Thrombo-embolism and Vascular Fragility in the Hamster Cheek Pouch After Anticoagulants, Blood **8**: 140, 1953.
6. Shulman, M. H., Alexander, L., Ehrentheil, O. F., and Gross, R.: Capillary Resistance Studies in Multiple Sclerosis, J. Neuropath. & Exper. Neurol. **9**: 420, 1950.
7. Lutz, B. R., Fulton, G. P., Young, G., Shulman, M. H., and Berman, H. J.: Petechial Formation in the Cheek Pouch of the Hamster *(Mesocricetus auratus)*, Federation Proc. **12**: 92, 1953.
8. Fulton, G. P., Lutz, B. R., Joftes, D. L., and Maynard, F. W.: Effects of Beta and X-irradiation on the Circulation in the Hamster Cheek Pouch (Motion Picture), Federation Proc. **11**: 52, 1952.
9. Knisely, M. H., Stratman-Thomas, W. K., and Eliot, T. S.: Capillary Circulation in the Malaria-Infected Monkey, Anat. Rec. **79**: 90, 1941.
10. Knisely, M. H., Bloch, E. H., Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**: 431, 1947.
11. Lutz, B. R.: Intravascular Agglutination of the Formed Elements of Blood, Physiol. Rev. **31**: 107, 1951.
12. Shwartzman, G., Schneierson, S. S., and Soffer, L. J.: Suppression of the Phenomenon of Local Tissue Reactivity by ACTH, Cortisone, and Sodium Salicylate, Proc. Soc. Exper. Biol. & Med. **75**: 175, 1950.
13. Moon, V. H., and Tershakovec, G. A.: Influence of Cortisone Upon Acute Inflammation, Proc. Soc. Exper. Biol. & Med. **79**: 63, 1952.
14. Menkin, V.: Further Studies on Mechanism of Increased Capillary Permeability in Inflammation With the Aid of Cortisone and ACTH, Proc. Soc. Exper. Biol. & Med. **77**: 592, 1951.
15. Ebert, R. H.: In Vivo Observations on the Effect of Cortisone on Experimental Tuberculosis, Using the Rabbit Ear Chamber Technique, Am. Rev. Tuberc. **65**: 64, 1952.
16. Ashton, N., and Cook, C.: In vivo Observations of the Effects of Cortisone Upon the Blood Vessels in Rabbit Ear Chambers, Brit. J. Exper. Path. **33**: 445, 1952.

INHIBITION OF HISTAMINE DEATH IN PERTUSSIS-INOCULATED MICE BY DIBENZYLINE, AN ADRENERGIC BLOCKING AGENT

LEON S. KIND, PH.D., CHARLESTON, S. C.

A NUMBER of β-chloroethylamine derivatives chemically related to Dibenamine have been reported to be moderately or highly effective in diminishing several effects of histamine. α naphthylmethylethyl-β-chloroethylamine prevented histamine shock and anaphylactic shock in guinea pigs,[1] and inhibited completely or diminished the hypotensive action of histamine in dogs.[2] However, actual data concerning the antihistaminic properties of adrenergic blocking agents have been fragmentary. The present report will demonstrate that the adrenergic blocking agent Dibenzyline* (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine) inhibited histamine death in pertussis-inoculated mice. The advantages of using pertussis-inoculated, histamine-sensitive mice in the study of compounds which might be active against histamine have been discussed in a previous publication.[3]

EXPERIMENTAL

White, male, 17- to 23-gram mice were injected with 0.2, 0.1, and 0.1 ml. of *H. pertussis* vaccine† on each of three successive days. Six days after the last injection, control and test animals were challenged intraperitoneally with 25 mg./kg. of histamine diphosphate (equivalent to 3 LD_{50} doses). Test animals received 5, 10, or 25 mg./kg. of Dibenzyline prior to challenge doses of histamine. Histamine was injected two hours after the administration of 5 or 10 mg./kg. of Dibenzyline. Animals which were inoculated with 25 mg./kg. of Dibenzyline became so ill (33 per cent deaths) that the challenge dose of histamine was postponed for twenty-four hours. At this time, however, Dibenzyline still gave 100 per cent protection against 3 LD_{50} of histamine. Since some mice were challenged with histamine two hours after Dibenzyline, and others twenty-four hours after the administration of this adrenergic blocking agent, two sets of control animals were employed.

Dibenzyline solutions were prepared by dissolving the hydrochloride salt in 10 per cent propylene glycol made slightly acid (0.05N) with concentrated H_2SO_4. Appropriate concentrations of these solutions were injected subcutaneously in multiple areas of the back.

Mice injected with *H. pertussis* vaccine, as already described, were also protected, on the sixth day following the last injection of this vaccine, with 5 mg./kg. of Dibenzyline prior to intraperitoneal challenge doses of epinephrine.

Deaths were noted for twenty-four hours after the administration of either histamine or epinephrine.

From the Department of Bacteriology, Medical College of South Carolina, Charleston, S. C., aided by a grant from the National Institutes of Health.

Received for publication Aug. 10, 1953.

*Supplied through the courtesy of the Smith, Kline & French Laboratories.

†Supplied through the courtesy of Sharp & Dohme, Inc.

RESULTS

The data in Tables I and II indicate that as little as 5 mg./kg. of Dibenzyline protected pertussis-inoculated mice from the lethal effects of both histamine and epinephrine. Ten mg./kg. of Dibenzyline, administered two

TABLE I. INHIBITION OF HISTAMINE DEATH BY DIBENZYLINE, AN ADRENERGIC BLOCKING AGENT

GROUP	DOSE OF DIBENZYLINE MG./KG.	CHALLENGE DOSE OF HISTAMINE MG./KG.	SURVIVORS	DEATHS	TOTAL	% SURVIVAL
I*	25	25	12	0	12	100
II	—	25	2	15	17	12
III†	10	25	14	0	14	100
IV‡	5	25	10	2	12	83
V	—	25	3	9	12	25

*†Indicates statistical significance ($p = < 0.01$) when compared to respective untreated controls.

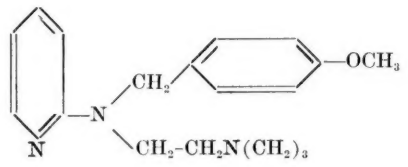
‡Indicates statistical significance ($p = 0.05$) when compared to untreated control group.

TABLE II. INHIBITION OF DEATH DUE TO EPINEPHRINE BY DIBENZYLINE, AN ADRENERGIC BLOCKING AGENT

GROUP NO.	DOSE OF DIBENZYLINE MG./KG.	CHALLENGE DOSE OF EPINEPHRINE MG./KG.	SURVIVORS	DEATHS	TOTAL	% SURVIVAL
I*	5	18	12	0	12	100
II	-	18	6	6	12	50

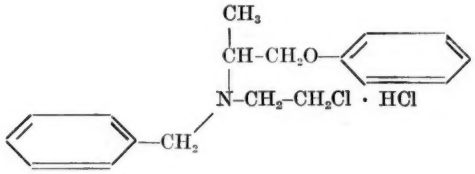
*Indicates statistical significance ($p = 0.05$) when compared with untreated control group.

hours before histamine, protected 100 per cent of the animals against 3 LD_{50} of this amine, while 25 mg./kg. of Dibenzyline exerted a protective effect (100 per cent survival) as long as twenty-four hours after its administration.



Neoantergan

(N-*p*-methoxybenzyl-N-dimethylaminoethyl-α aminopyridine)



Dibenzyline

(N-phenoxyisopropyl-N-benzyl-β-chloroethyl amine hydrochloride)

Fig. 1.

DISCUSSION

Dibenzyline, an adrenergic blocking agent used in the treatment of peripheral vascular disease and hypertension, appears to be a potent antihistaminic. The smallest dose of the compound which will protect pertussis-inoculated mice from the lethal effects of histamine is very similar to that previously reported for Neoantergan.[3] The structural similarities between Neoantergan and Dibenzyline are marked (Fig. 1).

Of particular interest is the fact that 25 mg./kg. of Dibenzyline protected 100 per cent of the animals twenty-four hours after its administration. The possibility that nontoxic doses of Dibenzyline and of other chemically related adrenergic blocking agents may exert antihistaminic effects for several days after their administration certainly warrants further investigation.

Although Dibenzyline has antagonistic effects against both epinephrine and histamine, it is unlikely that either of these effects is dependent on the other. Some antihistaminic drugs enhance the pressor effect of epinephrine, whereas others diminish or reverse the pressor response to epinephrine.[4] Neoantergan was ineffective in protecting pertussis-inoculated, histamine-sensitive mice from the lethal effects of epinephrine.[5] It has also been demonstrated that some adrenergic blocking agents possess no antihistaminic properties.[6]

SUMMARY

The adrenergic blocking agent, Dibenzyline, inhibited the lethal effects of both histamine and epinephrine in pertussis-inoculated, histamine-sensitive mice. Protection against histamine was obtained with doses similar to those reported for Neoantergan. Mice injected with 25 mg./kg. of Dibenzyline were protected from 3 LD_{50} of histamine administered twenty-four hours later.

REFERENCES

1. Achenbach, P., and Loew, E. R.: Antagonism to Histamine With Synthetic Compounds Which Exert Marked Epinephrine-Blocking Effects, Federation Proc. **6**: 304, 1947.
2. Loew, E. R., Micetich, A., and Achenbach, P.: Antagonism of the Excitatory Responses to Epinephrine and Adrenergic Nerve Stimulation With Benzhydryl-alkyl-β-chloroethyl Amines, Federation Proc. **6**: 351, 1947.
3. Kind, L. S.: Inhibition of Histamine Death in Pertussis-Inoculated Mice by Cortisone and Neoantergan, J. ALLERGY **24**: 52, 1953.
4. Loew, E. R.: The Pharmacology of Benadryl and the Specificity of Antihistamine Drugs, Ann. New York Acad. Sc. **50**: 1142, 1950.
5. Kind, L. S.: Unpublished observations.
6. Loew, E. R.: Pharmocology of Antihistamine Compounds, Physiol. Rev. **27**: 542, 1947.

THE DIURNAL VARIATION OF AIR-BORNE RAGWEED POLLEN AS DETERMINED BY A CONTINUOUS RECORDING PARTICLE SAMPLER AND IMPLICATIONS OF THE STUDY

RONALD DELAINE SMITH, M.S., AND ROLAND ROOKS, PH.D.,* IOWA CITY, IOWA

DURHAM[1] appears to have been the first to report a study on the hourly variation of ragweed pollen. In his study which was made during the height of the season, the conclusion was drawn that most of the day's yield of pollen was thrown into the air early in the morning at the usual time of the daily ripening of the male ragweed flowers and that by midnight the bulk of this load has been precipitated.

Wilmer and Marshall[2] concluded after exposure of slides for a two-hour period and with these slides collected over a twenty-four hour period that the atmospheric pollen content is less as the earth cools. The lowest counts were reported between 5:30 and 9:30 P.M.

The distribution of ragweed pollen in the upper atmosphere was studied by Heise and Heise[3] by exposing slides in the slip stream of a plane. "The data indicate that the level of maximum concentration rose from early afternoon until about 8:00 P.M. when the particles slowly fell until dawn, at which time there was ground fog. An analysis of these findings seems to indicate that the convection currents during the day and early evening are responsible for the lifting of the particles to high altitudes, and that the particles then sink as the ground cools off. . . . The importance of these observations is that they help explain the well-known fact that pollenosis is usually at its worst in the early morning hours."[3]

In a study by Barnes and Rooks[4] conducted for seven days on the diurnal pattern of pollen fall, slides were exposed on the standard gravity sampler[5] and were changed at intervals of six hours. The results showed that of the total pollen collected over twenty-four hour periods, 53 per cent was deposited on the slides between 6:00 A.M. and noon, 23 per cent from noon to 6:00 P.M., 14 per cent from 6:00 P.M. to midnight, and 10 per cent from midnight to 6:00 A.M. It was concluded that despite the fact that approximately three-fourths of the pollen is thrown into the air by the weeds in the daylight hours, the night air may contain large doses of pollen.

Jones[6] exposed four miscroscope slides coated with a thin film of petroleum jelly on a weather vane at about the height of the plant and concluded that the giant ragweed released 88 per cent of the average daily total between 8:00 and 11:30 A.M. during August 24 and 25 at Lincoln, Neb. Additional readings were taken at Stillwater, Okla., for four days during September, at which time it was found that about 95 per cent of the average daily total of giant ragweed was shed between 7:00 and 10:30 A.M.

Received for publication Aug. 14, 1953.

*Department of Hygiene and Preventive Medicine, College of Medicine, State University of Iowa.

Readings taken with the same sampler by Jones[6] in terms of Western ragweed at Stillwater for three days during September showed that maximum shedding occurred at 8:30 A.M. and that approximately 90 per cent of the average daily pollen supply was shed between 7:00 and 10:00 A.M.

In none of these reported studies was a volumetric device used, that is, sampling a known amount of air with some method for the removal of pollen as the air passes through the instrument. In all of the reported studies an adhesive, usually petroleum jelly was used to coat an ordinary microscope slide and this slide was then exposed to the air in the standard sampler or some slight modification thereof.

Durham[7] concluded that "in strong winds there are upward as well as downward currents and that wind impingement can, under such conditions be responsible for most of the 'gravity' catch."

Fletcher and Velz[8] state that "probably because of high degree of turbulence associated with variation in air movement, pollen grains actually land on an exposed slide more in accordance with the laws of chance than with laws of gravity."

Although certain volumetric devices have been reported, they have not been widely used in the study of aerial transmission pollen problems. Hawes, Small, and Miller[9] in 1942 reported a volumetric sampler by which the pollen was drawn through a fine slit opening and the pollen was inpinged onto an adhesive coated slide which was moved lengthwise by an electric clock mechanism. Fletcher and Velz[8] described a volumetric sampler developed by Hawes, Lang, and others by which the pollen is impinged onto a moving strip of adhesive tape. A similar device is described by Hall[10] and by Stenburg.[11] The sampler described by Stenburg[11] was selected for this problem because of its simplicity in operation, permanency of records, and the fact that long-time readings could be taken without any attention by the operator.

STATEMENT OF PROBLEM

This report is concerned with a study conducted on the diurnal variation of air-borne ragweed pollen as determined by a continuous recording particle sampler. Because of the sampling errors that do arise in connection with the exposure of a slide even in the standard sampler and due to the scarcity of reports and the small number of readings taken on the diurnal variation of ragweed pollen, it was believed further study of this problem would be of value, preferably by a volumetric sampler.

By the use of a suitable volumetric sampler during the entire ragweed season, it was hoped further information aside from the diurnal variation might be added to our present knowledge as to the general aerial dispersion of ragweed pollen.

PROCEDURE

The Ragweed Pollen Sampling Efficiency of the Continuous Recording Volumetric Sampler.—Although a few readings were taken by Stenburg[11] with the "continuous recording particle sampler" to determine the efficiency of this

instrument in sampling for pollen, no exact statement as to its efficiency was made. The conclusion was drawn, however, that "the efficiency of the instrument is high."

In the study here reported preliminary efficiency readings were taken with commercially collected ragweed pollen (*Ambrosia trifida*). This pollen was released from a flask by compressed air directly into the air intake of the sampler during its operation by the use of a suitable rubber tube connection. Petroleum-jellied slides attached to the sides and placed at the bottom within the sampler indicated that not all of the pollen was being collected on the tape but rather some was undergoing impingement within the instrument. Slide counts indicated that although there was no impingement of the pollen on the sides, the pollen was collecting at the bottom of the sampler.

Additional readings indicated that if a small dosage of pollen was placed within and on the floor of the instrument and air was passed through the sampler which was known to contain no ragweed pollen, some of this pollen within the instrument was impinged on the recording tape. For this reason, during actual use of this sampler during the ragweed season, the bottom of the instrument was thoroughly cleansed daily. The top portion of the instrument which was difficult to cleanse was sealed such that no pollen could collect in this area.

In all efficiency tests and during actual operation of the sampler during the ragweed season, the distance between the impinger and tape was set at one-sixteenth of an inch. With a suitable opening for cooling of the motor and with this distance of one-sixteenth of an inch between the impinger and the tape, the air flow through the instrument was calibrated at 0.5 cu. ft. per minute. This rate of air flow was maintained in all preliminary readings as well as during operation of the sampler through the ragweed season.

In additional experiments on efficiency the pollen was released in a similar manner to the above procedure directly into the intake of the instrument while the continuous recording particle sampler was in operation. The air which passed through this instrument under test was led directly by a suitable connection into another sampler.[12] This connection was kept as short as possible (6 inches in length) to minimize impingement within this tube. That very little if any impingement did occur within this connection was indicated by the fact that there was no gradual increase in pollen counts by the second sampler with an increase in the number of readings. The rate of air flow through both samplers was maintained by a vacuum pump at 0.5 cu. ft. per minute and 1 cu. ft. air samples were taken on all efficiency readings.

In all readings on efficiency, petroleum-jellied slides were placed on the floor of the instrument to determine impingement within the sampler. One square centimeter slide area was counted for each reading and these readings were taken into consideration in computation of the efficiency.

The efficiency of the continuous recording particle sampler under the above sampling conditions was found to be 76 per cent. This, because of the high pollen dosage used on each test (300 to 1,000 pollen granules per cubic yard of air), undoubtedly represents the minimum efficiency of this sampler. This

figure compares favorably with a previous report[12] when under similar sampling conditions for ragweed pollen the efficiency was reported as 69 per cent when impingement to petroleum-jellied slides was compared with electrostatic precipitation. The somewhat higher efficiency when impingement occurs to tape may very well be due to the better adhesive qualities of tape* as compared with petroleum jelly.

Location and Operation of the Volumetric Sampler During the Ragweed Season.—The sampler was located on the topmost ledge of a tower on the Medical Laboratories Building, approximately 75 feet above the ground. This site placed the sampler well above any near-by trees with no obstructions to lateral air currents from any direction. The sampling site is also quite distant from any known ragweed source.

The sampler was kept in continuous operation, except for the small amount of time occasionally necessary to change the roll of tape and for the daily removal of that tape representing a twenty-four hour reading. Air samples were collected from Aug. 7 through Sept. 20, 1952. This represents the usual ragweed season in this area.

On three days the rainfall was so heavy as to destroy entirely the twenty-four hour reading. Although the intake into this sampler is protected, during a heavy rain, moisture of sufficient quantity is drawn into the instrument to destroy entirely the adhesive qualities of the tape.

DISCUSSION AND RESULTS

Hourly Variation in the Aerial Transmission of Ragweed Pollen on a Seasonal Basis.—Fig. 1 indicates that on a seasonal basis the peak incidence of ragweed pollen is reached from 11 to 12 A.M. This peak incidence amounting to 22.8 per cent of all the pollen collected for a twenty-four hour period is 57 times the dosage encountered by the individual during exposure for any single early morning hour from 3 to 6 A.M.

The hours from 10:00 A.M. to 1:00 P.M. account for 56 per cent of the pollen collected for the twenty-four hour period. This pollen dosage represents 23 times the exposure of the patient for the same time interval but from 6:00 to 9:00 A.M. Similarly, the pollen dosage from 10 A.M. to 1:00 P.M. accounts for 25 times the exposure of the individual during the hours from 9 to 12 midnight.

Hourly Variation in the Aerial Transmission of Ragweed Pollen During the Month of August.—Eighty-six per cent of the pollen collected on a seasonal basis from August 7 through September 20 was collected during the month of August.

Fig. 2 indicates that 21 per cent of the pollen obtained during this month was collected from 10:00 to 11:00 A.M. and 67 per cent was collected from 9:00 A.M. to 1:00 P.M.

*Scotch cellophane tape, ¾ inch by 300 inches (Minnesota Mining & Mfg. Co., Saint Paul 6, Minn.).

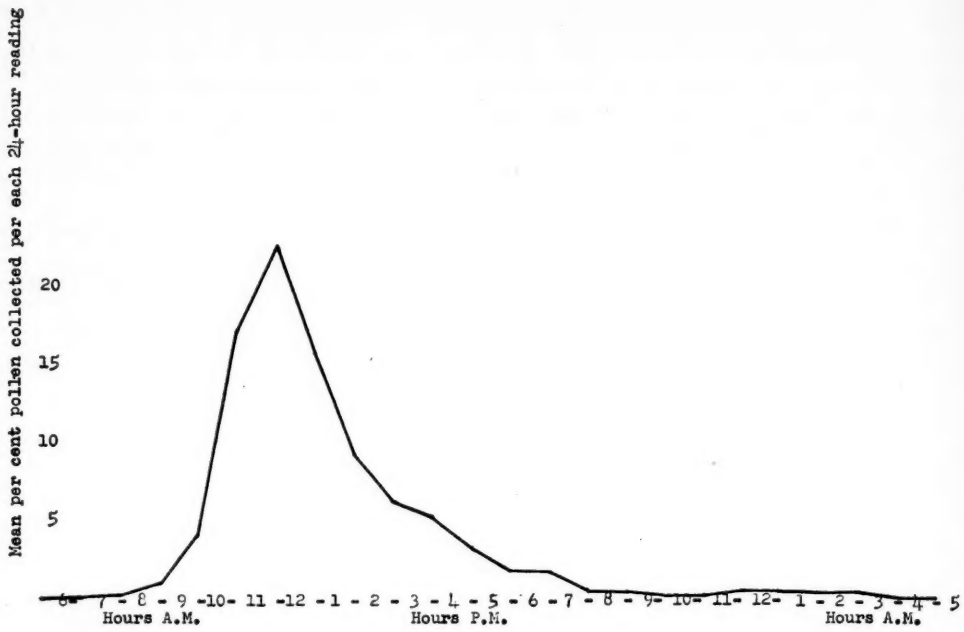

Mean per cent pollen collected per each 24-hour reading
20
15
10
5
6 - 7 - 8 - 9 -10- 11 -12 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9- 10- 11- 12- 1 - 2 - 3 - 4 - 5
Hours A.M.
Hours P.M.
Hours A.M.

Fig. 1.—Hourly variation in air-borne ragweed pollen August 7 through September 20, Iowa City, Iowa, 1952. Each hourly reading indicates on a seasonal basis the mean per cent pollen collected per each twenty-four hour readings.

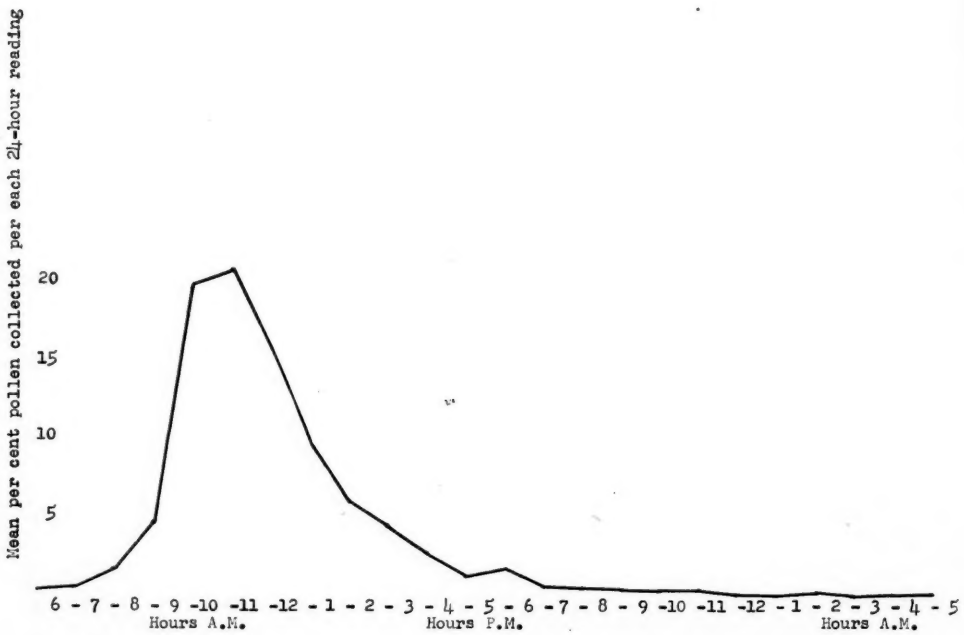

Mean per cent pollen collected per each 24-hour reading
20
15
10
5
6 - 7 - 8 - 9 -10 -11 -12 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 -10 -11 -12 - 1 - 2 - 3 - 4 - 5
Hours A.M.
Hours P.M.
Hours A.M.

Fig. 2.—Hourly variation in air-borne ragweed pollen August 7 through August 31, Iowa City, Iowa, 1952. Each hourly reading indicates the mean per cent pollen collected per each twenty-four hour reading during the month of August.

The fall in the afternoon again occurs very rapidly and the incidence from 6:00 in the evening until 6:00 in the morning is practically the same during the month of August as compared with the incidence on a seasonal basis.

Hourly Variation in the Aerial Transmission of Ragweed Pollen During the Month of September.—September accounted for 14 per cent of the seasonal pollen collected. One might infer because of the low total for this month that hourly recordings would show marked changes as compared with the month of August.

Fig. 3, however, again indicates a sharp increase in the ragweed pollen incidence during the morning hours with 50 per cent collected between the hours of 9:00 A.M. and 1:00 P.M.

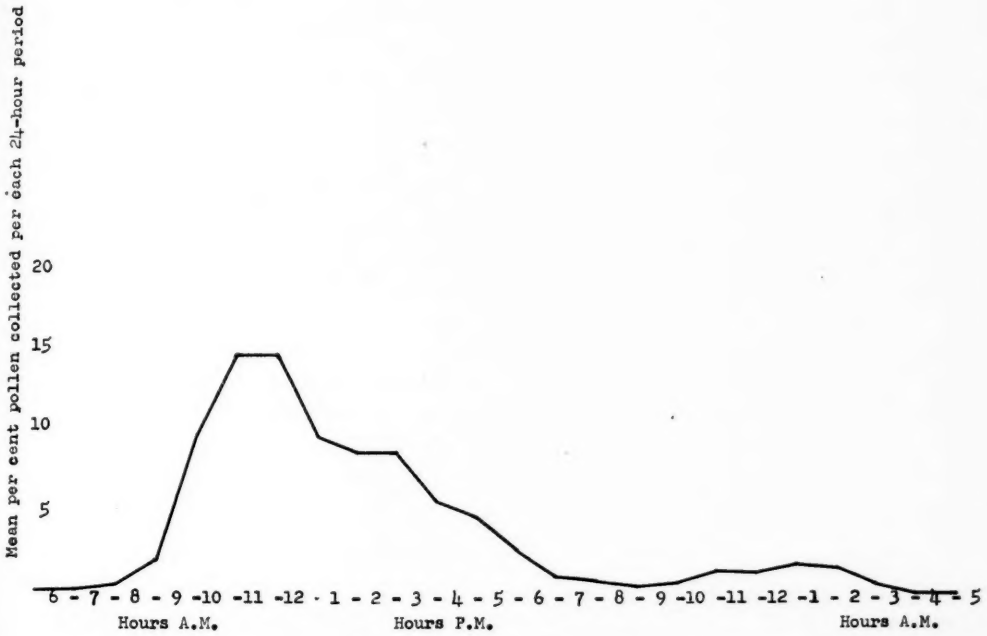

Mean per cent pollen collected per each 24-hour period
20
15
10
5
6 - 7 - 8 - 9 -10 -11 -12 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 -10 -11 -12 -1 - 2 - 3 - 4 - 5
Hours A.M.
Hours P.M.
Hours A.M.

Fig. 3.—Hourly variation in air-borne ragweed pollen September 1 through September 20, Iowa City, Iowa, 1952. Each hourly reading indicates the mean per cent pollen collected per each twenty-four hour reading during the month of September.

Although the reported rainfall for the month of September was only 0.94 inch, the pollen incidence was again extremely low from 6:00 P.M. to 6:00 A.M.

It has been reported previously[4] that in this area (Iowa City, Iowa) during seven pollen seasons, the apex date or peak daily incidence varied from August 21 to September 1. This, together with the fact that 86 per cent of the pollen is released during August, suggests that if pollen undergoes a marked redistribution after it has once settled upon trees, shrubs, and buildings, it should certainly occur during the month of September and especially when the month is characterized by a lack of rainfall. If such a redistribution does occur, it does not happen at night.

Daily Variation in the Aerial Transmission of Ragweed Pollen on a Seasonal Basis.—Volumetric air samples during the pollen season of 1952 when compared with pollen counts of slides exposed in a standard gravity sampler located at the same sampling site showed the same type curve when comparisons were made on a daily basis. Beginning with August 7 and with each additional day there was the usual marked increase in the pollen concentration of the air, but the peak incidence was reached with the standard sampler on August 26. The apex date using the volumetric sampler was August 28. After August 28 there was the usual irregular fall in incidence so characteristic of the ragweed problem.

There was close agreement in the first detection of air-borne ragweed pollen by the usual slide method as compared with the volumetric samples. Similarly, the close of the season was practically the same, at which time few or no pollen grains were sampled by either method. These comparisons indicate that volumetric air samples do not have any particular advantages over the standard gravity sampler in indicating the beginning, the end, and the apex date of the pollen season.

Meteorological Factors in Ragweed Distribution and Prevalence.—It has been previously reported[13] that under experimental conditions the settling rate of ragweed pollen is increased with an increase in humidity. Duke[14] reports that "pollen settles out of the air in the same way that mud settles out of water, so that air which has been still for a time is practically free from pollen." It is difficult to determine by means of the standard gravity sampler if the reported low pollen counts (1, 2, and 4) in the evening and night are due to the natural increase in the humidity or to the natural decrease in wind velocity or both. A sampling error does arise in the use of the standard sampler in that the pollen catch would be proportionately less in the evening and night. This is due to the fact that the pollen count in terms of this sampler is dependent in large part upon the passage of lateral air currents over the exposed slide.[7]

A comparison of the pollen incidence in terms of volumetric air samples shows that 47.0 per cent of the pollen collected on a seasonal basis was collected from 6:00 A.M. to 12 noon, 43.6 per cent from 12 noon to 6:00 P.M., 5.8 per cent from 6:00 P.M. to 12:00 midnight, and 3.6 per cent from 12 midnight until 6 in the morning. It is believed these readings reflect in part the importance of humidity in determining the settling rate of pollen. The mean relative humidity in percentage at 6:00 A.M. on a seasonal basis was 94 per cent while at 12:00 midnight it was 88 per cent. The lowest relative humidity reading was 51 per cent at 12:00 noon when the pollen counts are highest and by 6 in the evening the relative humidity had increased to 68 per cent.

That this marked variation throughout the day and night in pollen incidence is largely due to a change in the humidity rather than to a change in wind velocity is shown by these additional comparisons. It has been shown by Crawford[15] that a horizontal air flow of 1.58 cm. per second (0.035 miles per hour) would be sufficient to overcome the force of gravity and produce air-borne pollen. The mean wind velocity for August and September at 12 noon in the study here reported was 11 miles per hour. The mean wind velocity

for the other six-hour intervals was from 5 to 6 miles per hour. This comparatively low wind velocity at night would be ample to overcome the force of gravity and produce air-borne pollen according to the experimental results of Crawford.

This discussion has so far neglected still another factor in the aerial transmission of ragweed pollen. As the earth's surface is warmed, rising convection air currents are formed. With a cooling of the earth's surface, downward air currents are produced and with an unequal warming of the earth's surface marked air turbulence results.

The mean dry bulb reading during the months of August and September was 78 at noon. By evening at 6:00 the mean dry bulb reading was 71. Meanwhile the proportion of pollen collected during the season (Fig. 1) had dropped from a peak of 22.8 per cent from 11 to 12 noon to only 2.2 per cent from 5:00 to 6:00 P.M. The slight difference in temperature at noon as compared with 6:00 in the evening, a difference of 7°, could hardly account for any large part of this rapid drop in the incidence of ragweed pollen.

It has been pointed out by Durham[1] that most of the day's yield in pollen is "thrown into the air early in the morning at the usual time of the daily ripening of the male ragweed flowers," with the bulk of this pollen released from the individual plants by 12:00 noon as shown by these results. Although with a sudden gust of wind the entire day's production of pollen by the individual plant may be released in just a few minutes,[8] the gradual increase as shown in the figures suggests our sampler was sufficiently distant from any ragweed source to minimize this factor.

A comparison of these volumetric counts with wind direction revealed no differences. It would have been of interest to have determined volumetrically the exact percentage of pollen removed from the air by a given amount of rain. This, as has been previously mentioned, was impossible due to the moisture accumulation within the instrument during rain which destroyed the adhesive qualities of the collecting tape.

IMPLICATIONS OF THE STUDY

Maintaining a Low Pollen Refuge.—It has been reported by Barnes and Rooks[16] that "the total daily pollen exposure even during the worst ragweed seasons and in the worst ragweed areas can be kept at a low and oftentimes even subclinical level." This was accomplished by the use of suitable window type pollen filtering units along with certain precautions against entrance of pollen into this refuge by air-dried laundry, outer clothing worn by members of the family, family pets, bouquets from the flower garden, etc.

In maintaining such a pollen refuge the most critical period during the day for entrance of pollen from the outdoors through open doors and windows would be from 9:00 A.M. to 1:00 P.M. during both the months of August and September. The second period of greatest danger would be the period from 1:00 P.M. to 6:00 P.M. From 6:00 P.M. until 6:00 A.M. the pollen dosage of outdoor air is so low as to be of much less significance if the home or pollen refuge is opened to outdoor air.

For those not able to afford the purchase of a commercial window type filtering unit, a pollen refuge could be established which would be effective and much less costly than would be the purchase of these units. An exhaust fan could be installed, either in the attic or in a window, and all outdoor air could then be filtered by installation of suitable air filters in certain windows in the home with all other windows and all doors kept tightly closed at all times. Volumetric air samples taken in a home during the ragweed pollen season in 1952 indicated that it was possible by this method to reduce the number of pollen granules to 5 or less per cubic yard of air. With this method of pollen control the air will enter the home at the place of lowest resistance so that full cooperation of other members of the family is essential from the standpoint of open doors, especially from 6:00 A.M. to 6:00 P.M.

The refuge should first undergo a thorough cleansing prior to the pollen season to prevent a carry-over of pollen from previous summers. A circular fan could be safely used at any time indoors to add to comfort provided the cleansing prior to the season has been thorough.

A person during the evening and early morning hours might take advantage of the outdoors for a time, provided the activity of the individual did not again create a pollen exposure problem. Mowing the lawn, working in the garden, a ride in the family car even in the evening could significantly increase the pollen exposure of the individual. Volumetric air samples taken within a car after brushing the upholstering have shown readings sufficient to produce clinical symptoms long after the pollen season.

Both of these methods can be used successfully with definite benefit to the individual patient in that the pollen exposure is significantly lessened. It is obvious that both of these methods would make more beneficial the treatment methods utilized by the physician.

In Desensitization.—The wide diurnal variation of ragweed pollen is also of some importance in attempts at desensitization. As has been previously reported,[16] "the number of pollen granules inspired by an individual is not a direct multiple of the number reported per cubic yard of air." In terms of the standard sampler it was calculated in this previous report[16] that the pollen catch on a seasonal basis during the period from 6:00 P.M. to 6:00 in the morning was 25 per cent. Actually the pollen incidence as shown by volumetric readings is much lower, more nearly 10 per cent, while the pollen incidence is higher during the hours from 6:00 A.M. to 6:00 in the evening (90.6 per cent) than the incidence in terms of the standard sampler which was reported as approximately 50 per cent. The number of pollen granules inspired during a twenty-four hour period is actually much higher than would otherwise be expected unless this marked fluctuation in ragweed pollen incidence is recognized. This high incidence of ragweed pollen between the hours from 9:00 A.M. to 1:00 P.M., especially during the month of August, may make especially difficult attempts at desensitization or other treatment procedures.

SUMMARY

A continuous recording volumetric sampler was placed in operation during the entire ragweed season after the efficiency of this sampler was determined in terms of *Ambrosia trifida.*

An analysis of these twenty-four hour volumetric air samples revealed:

1. The most critical period in exposure of the patient to ragweed pollen is during the hours from 9:00 A.M. to 1:00 P.M. Sixty-seven per cent of the pollen collected during the month of August was collected from 9:00 A.M. to 1:00 P.M. Fifty per cent of the pollen collected during the month of September was collected during this same time period.

2. Only 10 per cent of the pollen collected for the twenty-four hour periods was collected from 6:00 P.M. to 6:00 A.M. during the months of August and September.

3. A comparison of volumetric air samples with ragweed pollen counts made with a standard sampler located at the same sampling site shows no particular advantages in the use of a volumetric sampler in indicating the beginning, the end, and the apex date of ragweed pollen.

4. Certain meteorological factors in determining the ragweed pollen incidence are mentioned and the implications of this study are discussed.

REFERENCES

1. Durham, Oren C.: Cooperative Studies in Ragweed Pollen Incidence, Atmospheric Data From Twenty-two Cities, J. ALLERGY **1**: 12, 1929.
2. Wilmer, Harry B., and Marshall, Herbert: A Note on the Quantitative Survey of Pollen, J. ALLERGY **3**: 63, 1931.
3. Heise, Herman A., and Heise, Eugenia R.: The Distribution of Ragwed Pollen and Alternaria Spores in the Upper Atmosphere, J. ALLERGY **19**: 403, 1948.
4. Barnes, Milford E., and Rooks, Roland: Ragweed Pollinosis; Some Practical Considerations, J. Iowa State Med. Soc. **40**: 287, 1950.
5. Durham, Oren C.: The Volumetric Incidence of Atmospheric Allergens. IV. A Proposed Standard Method of Gravity Sampling, J. ALLERGY **17**: 79, 1946.
6. Jones, Melvin D.: Time of Day of Pollen Shedding of Some Hay Fever Plants, J. ALLERGY **23**: 247, 1952.
7. Durham, Oren C.: Aerobiology: Development and Technic, chap. 42, p. 457, in Vaughn, Warren T., and Black, J. Harvey: Practice of Allergy, St. Louis, 1948, The C. V. Mosby Company.
8. Fletcher, Alfred H., and Velz, C. J.: Pollens-Sampling and Control, Indust. Med. **19**: 129, 1950.
9. Hawes, Roland C., Small, Willard S., and Miller, Hyman: An Apparatus for Determining the Pollen Content of Air and Notes on Pollen Survey Methods, J. ALLERGY **13**: 474, 1942.
10. Hall, Lawrence B.: The Equipment Development Section of the Technical Development Services, CDC Bulletin **9**: 22, 1950.
11. Stenburg, R. L., and Hall, Lawrence B.: A Continuous Recording Particle Sampler, Mimeographed Notes, CDC Center, Technical Development Services, Public Health Service, Federal Security Agency, Atlanta 5, Ga.
12. Rooks, Roland: A Device for the Electrostatic Precipitation of Pollen and Fungus Spores Upon a Counting Slide, J. ALLERGY **19**: 206, 1948.
13. Shapiro, Richard S., and Rooks, Roland: The Accuracy of the Reported Ragweed Pollen Count as a Measure of the Actual Pollen Exposure of Individuals in That Community, J. ALLERGY **22**: 450, 1951.
14. Duke, W. W.: The Pollen Content of Still Air, J. A. M. A. **91**: 1709, 1928.
15. Crawford, James H.: Determination of the Specific Gravity of Ragweed Pollen (Ambrosia elatior) and Conversion of Gravity Sample Counts to Volumetric Incidence, Pub. Health Rep. **64**: 1195, 1949.
16. Barnes, M. E., and Rooks, Roland: Pollen Refuge at Home, J. Iowa Med. Soc. **36**: 190, 1946.

REACTIONS FOLLOWING THE USE OF BACITRACIN, TYROTHRICIN, GRAMICIDIN, AND POLYMIXIN B TROCHES: A CONTROLLED STUDY

AUSTIN H. KUTSCHER, D.D.S., JACK BUDOWSKY, D.D.S., AND NEAL W. CHILTON, D.D.S., M.P.H., NEW YORK, N. Y.

THE authors have previously reported in this JOURNAL[1, 2] on the incidence and types of reactions following the use of terramycin, aureomycin and procaine penicillin G troches. These studies stemmed from the widespread evidence of local and systemic side effects observed during antibacterial therapy.[3-17] The incidence of reactions to bacitracin, gramicidin, tyrothricin, and polymixin B troche medication has not been reported. The present study was intended to evaluate the reactions which might result from the administration of these four antibiotics in troche form, and to compare the incidence and types of such reactions with those previously observed by us in the terramycin, aureomycin, and procaine penicillin G troche studies.

METHODS

Group I was composed of 20 normal subjects, aged 23 to 27, all men, comprising a volunteer group of dental students. Four troches per day, each containing 1,000 units (0.1 mg.) of bacitracin, were administered to each subject until 10 troches had been allowed to dissolve completely in the mouth.

Group II was composed of 80 patients, aged 16 to 58, 27 male and 53 female, who were treated for various types of minor oral disorders with bacitracin troches (1,000 units per troche), 5 troches per day for four days.

Group III, a control group for the bacitracin study, was composed of 50 patients, aged 18 to 61, 16 male and 34 female, similar to those in Group II. This group was treated exactly as Group II except that placebo troches were administered 5 per day for four days. Placebo troches were identical in content and appearance with the medicated troches except for the inert filler which replaced the active ingredient, bacitracin,

Group IV was composed of 17 normal subjects, aged 23 to 28, all male, comprising a volunteer group of dental students. Four troches per day each containing 1 mg. of tyrothricin were administered to each subject until 10 troches had been allowed to dissolve completely in the mouth.

From the Divisions of Research (Hannah and Harry Posner Research Laboratory) and Diagnosis of the School of Dental and Oral Surgery and the School of Public Health of the Faculty of Medicine, Columbia University.

Bacitracin troches and placebos as well as tyrothricin troches and placebos for this study were supplied through the courtesy of Dr. Gilbert Bayne of Sharp & Dohme, Inc., West Point, Pa. Bacitracin troches and placebos were also supplied by the Commercial Solvents Corp., Terre Haute, Ind.

Gramicidin troches (Gramolets) were supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. George Babcock.

Polymixin B-bacitracin troches were supplied by Chas. Pfizer & Co., Inc., Brooklyn, N. Y., through the courtesy of Dr. W. Alan Wright and Mr. George Penny.

Received for publication Sept. 14, 1953.

TABLE I. TYPE, FREQUENCY, AND SEVERITY OF REACTIONS TO BACITRACIN, TYROTHRICIN, POLYMIXIN B-BACITRACIN, AND GRAMICIDIN TROCHES

REACTIONS	BACITRACIN									TYROTHRICIN									POLYMIXIN B-BACITRACIN									GRAMICIDIN		
	GROUP I			GROUP II			GROUP III (PLACEBO)			GROUP IV			GROUP V			GROUP VI (PLACEBO)			GROUP VII			GROUP VIII			GROUP IX (PLACEBO)			GROUP X		
	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+
Abdominal ache and pain				1												1						1								
Aggravation of symptoms																														
Aphthae													1																	
Cheilosis																														
Constipation																														
Diarrhea				1			1			1						1									1					
Dizziness																														
Drowsiness	1			1												1														
Fever																														
Flatulence	1												1									1								
Glossitis																														
Headache										1																				
Increased freq. of stool				1									1																	
Intestinal upset				1			1			1						1									1					
Joint pains																														
Loose stool				1									2						1											
Malaise																												1		
Nausea	1						2			1			3			2			1			2		1	2			2		
Pharyngitis																														
Pruritus ani																														
Rectal burning																														
Stomatitis																														
Taste disturbance		4		4			3			2			4			3			2			2			3			3		
Tiredness				1			1																		1					
Vomiting																														
Total no. reactions	7	0	0	11	0	0	8	0	0	6	0	0	12	0	0	9	0	0	4	0	0	6	0	1	8	0	0	6	0	0
Total no. reactions in group		7			11			8			6			12			9			4			7			8			6	
Total no. patients in group		20			80			50			17			83			50			20			80			50			50	
Total no. patients showing react.		4			7			5			4			8			6			3			6			5			4	

1+ = reported, but not inconveniencing.
2+ = moderate, uncomfortable but not forcing discontinuation of therapy.
3+ = severe, forced discontinuation of therapy.

TABLE II. COMPARISON OF REACTIONS TO BACITRACIN, TYROTHRICIN, POLYMIXIN B,

	BACITRACIN						TYROTHRICIN						POLYMIXIN B					
	GROUPS I & II			GROUP III (PLACEBO)			GROUPS IV & V			GROUP VI (PLACEBO)			GROUPS VII & VIII			GROUP IX (PLACEBO)		
REACTIONS	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+
Abdominal ache and pain	1									1			1					
Aggravation symptoms																		
Aphthae							1											
Cheilosis																		
Constipation																		
Diarrhea	1			1			1			1						1		
Dizziness																		
Drowsiness	2									1								
Fever																		
Flatulence	1						1						1					
Glossitis																		
Headache							1											
Increased freq. of stool	1						1											
Intestinal upset	1			1			1			1						1		
Joint pains																		
Loose stool	1						2						1					
Malaise																		
Nausea	1			2			4			2			3		1	2		
Pharyngitis																		
Pruritus ani																		
Rectal burning																		
Stomatitis																		
Taste disturbance	8			3			6			3			4			3		
Tiredness	1			1												1		
Vomiting																		
Total no. reactions	18	0	0	8	0	0	18	0	0	9	0	0	10	0	1	8	0	0
Total no. reactions in groups		18			8					18	9			11			8	
Total no. patients in groups		100			50					100	50			100			50	
Total no. patients showing reaction		11			5					12	6			9			5	
Percentage of patients showing reactions		11%			10%					12%	12%			9%			10%	

Group V was composed of 83 patients, aged 21 to 55, 33 male and 50 female, who were treated for various types of minor oral disorders with tyrothricin troches (1 mg. tyrothricin per troche), 5 troches per day for four days.

Group VI, a control group for the tyrothricin study, was composed of 50 patients, aged 19 to 49, 18 male and 32 female, similar to those in Group V. This group was treated exactly as Group V except that placebo troches were administered 5 per day for four days. Placebo troches were identical in content and appearance with the medicated troches except for the inert filler which replaced the active ingredient tyrothricin.

Group VII was composed of 20 normal subjects, aged 20 to 26, 13 male and 7 female, comprising a volunteer group of students. Five troches per day each containing polymixin B and bacitracin (1,000 units of polymixin B and 50 units of bacitracin per troche) were administered to each subject for four days.

GRAMICIDIN, TERRAMYCIN, AUREOMYCIN, AND PROCAINE PENICILLIN G TROCHES

GRAMICIDIN GROUP X			TERRAMYCIN GROUPS (MEDICATED)			TERRAMYCIN GROUP (PLACEBO)			AUREOMYCIN GROUPS (MEDICATED)			AUREOMYCIN GROUP (PLACEBO)			PROCAINE PENICILLIN G GROUPS (MEDICATED)			PROCAINE PENICILLIN G GROUP (PLACEBO)		
1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+	1+	2+	3+
			9	1	1				2								1			
			1	1											2					
									1		2									
			2																	
			3						1						1					
			27	11	7	1			6	5	4				1		3			
				1					1				1							
			4			1			6						4					
			1	2											1					
			20	5		1	10		7	2		1			3	2		2		
				2	4				4		3				5		2			
			4	1		1			4	1						1				
			4						3						4					
			3	3					4						3					
			3												2					
			7	2		2			7			1			5	1		1		
1			6						3			1			3			2	2	
2			25	8	3	7		1	11	6	6	5	2		9	5	4			
			2		3				2		2				2					
			3	5					2	3					1	1				
			1						4											
			1	1	4				3		3				1		4			
3			4	4		3			22	4	1	3			21	4		3		
			2						7						3		1			
			1		1				1						1					
6	0	0	133	47	23				101	21	21	11	3	0	72	14	15	8	2	0
	6		203						143			14			101			10		
	50		143						100			50			100			50		
	4		76						51			7			38			7		
	8%		53%						51%			14%			38%			14%		

Group VIII was composed of 80 patients, aged 15 to 54, 31 male and 49 female, who were treated for various types of minor oral disorders with the polymixin B-bacitracin troches, 5 troches per day for four days.

Group IX, a control group for the polymixin B-bacitracin study, was composed of 50 patients, aged 16 to 51, 32 male and 28 female, similar to those in Group VIII. This group was treated exactly as Group VIII except that placebo troches were administered 5 per day for four days. The placebo troches used in this study were identical in content and appearance to the medicated troches except for the absence of the active ingredient, polymixin B and bacitracin.

Group X was composed of 50 patients, aged 18 to 56, 18 male and 32 female, who were treated for various types of minor oral disorders with gramicidin troches (0.25 mg. per troche), 5 troches per day for three days. There was no placebo control group for gramicidin since placebos for the bacitracin troches were substantially the same as the gramicidin troches.

A careful history concerning previous experience with antibacterial agents, reactions to previous antibiotic therapy, drug sensitivity, and other allergies was obtained from each patient. During and after the completion of therapy, each patient was examined orally and specifically questioned as to whether any reaction of any type had been noted. If a reaction was observed or reported, the patient was queried in detail concerning the character and severity of the reaction(s) which had been manifested.

RESULTS

The types, frequency, and severity of reactions observed during and after bacitracin, tyrothricin, gramicidin, polymixin B-bacitracin, and placebo control troche therapy are detailed and summarized in Table I. Reactions were graded as follows:

1+ = reported, but not inconveniencing
2+ = moderate, uncomfortable but not forcing discontinuation of therapy
3+ = severe, forced discontinuation of therapy

In this study it will be noted that with one exception (severe nausea with polymixin B-bacitracin) all reactions were of grade 1+ severity. A summary of the reactions noted and those reported in the two previous articles in our series appears in Table II. It will be noted that the range of percentage of patients showing reactions with the four antibiotic preparations and the three placebos studied here is very small (8 to 12). The percentages of patients showing reactions in the present study are quite similar to those observed for the placebo troches used in our previous studies[1, 2] (10.7 to 14) and are very much less than the percentages determined for terramycin (53 per cent), aureomycin (51 per cent), and procaine penicillin G troches (38 per cent). When the over-all percentage of patients showing reactions following the use of bacitracin. tyrothricin, polymixin B, and gramicidin troches is compared with that following the use of aureomycin, procaine penicillin, and terramycin troches pooled together, a statistically significant difference is obtained.

TABLE III. SUMMARY OF HISTORIES OF PREVIOUS MEDICATION OF PATIENTS INGESTING BACITRACIN, TYROTHRICIN, POLYMIXIN B-BACITRACIN, GRAMICIDIN, TERRAMYCIN, AUREOMYCIN, AND PROCAINE PENICILLIN G TROCHES

DRUG	NO. OF CASES STUDIED	SPECIFIC ANTIBIOTIC ADMINISTERED TO THE GROUP HAD PREVIOUSLY BEEN ADMINISTERED TO PATIENT (RECOLLECTED BY PATIENT)				PREVIOUS REACTION NOTED OR RECOLLECTED BY PATIENT TO THE DRUG			
		SYSTEMIC	TOPICAL	TOTAL	#	SYSTEMIC	TOPICAL	TOTAL	#
Terramycin	143	5	0	5		0	0	0	
Aureomycin	100	18	12	28		2	4	6	
Procaine penicillin	100	63	20	73		2	2	4	
Bacitracin	100	0	2	2		0	0	0	
Tyrothricin	100	0	8	8		0	0	0	
Polymixin B	100	0	0	0		0	0	0	
Gramicidin	50	0	1	1		0	0	0	

Tabulations of the histories of the four groups compared in this study and also of the three groups previously reported (terramycin, aureomycin, procaine

TABLE IV. COMPARISON OF THE AVERAGE NUMBER OF REACTIONS SEEN WITH BACITRACIN, TYROTHRICIN, POLYMIXIN B-BACITRACIN, GRAMICIDIN, AUREOMYIN, PROCAINE PENICILLIN G AND TERRAMYCIN TROCHES

	BACITRACIN		TYROTHRICIN		POLYMIXIN B-BACITRACIN		GRAMICIDIN		AUREOMYCIN		PROCAINE PENICILLIN G		TERRAMYCIN	
	AVE.	S.E.*	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.	AVE.	S.E.
Reactions per patient	0.180	0.084	0.180	0.077	0.11	0.048	0.12	0.052	1.43	0.032	1.01	0.023	1.42	0.016
Reactions per reactor	1.64	0.606	1.50	0.493	1.22	0.539	1.50	0.581	2.80	0.051	2.66	0.046	2.67	0.013

*S.E. is the standard error of the average, and is calculated as S.E. $= \sigma / \sqrt{N}$, where σ is the standard deviation and N is the number of patients.

penicillin G) appear in Table III. Since the patients had not been studied at the time of previous treatment specifically for toxic reactions, and since the administration of the drug had in most cases been many months in the past, the reported incidence of previous reactions is subject to question, and in any event probably would be understandably smaller than those reported herein. Also, the accuracy of patients' recollection of previous therapy and reactions is questionable.

A comparison of the average number of reactions per patient and per reactor for all the four antibiotics studied at this time and for the three antibiotics studied previously appears in Table IV. Again it will be noted that terramycin, aureomycin, and penicillin G troches tend to be similar, while bacitracin, tyrothricin, polymixin B, and gramicidin tend to group together with respect to these averages. Roughly, the average number of reactions per patient are about ten times greater per patient for aureomycin, penicillin, and terramycin than for bacitracin, tyrothricin, polymixin B, and gramicidin; and about twice as great in terms of the average number of reactions per reactor.

In the present investigation, in contrast to the terramycin, aureomycin, and procaine penicillin G studies, the reactions, although limited primarily to the gastrointestinal tract, did *not* include the oral cavity, pharyngeal passageway, rectum, or anus. Glossitis, stomatitis, or pharyngitis did not occur in any case in the bacitracin, tyrothricin, gramicidin, or polymixin B-bacitracin groups. Reactions noted in the remaining portions of the gastrointestinal tract were considerably milder in nature for the troches studied at this time than those reported previously in the terramycin, aureomycin, and procaine penicillin G studies, and were significantly less frequent. No occurrence of delayed gastrointestinal reactions was reported. Diarrhea was rare and was not accompanied in any instance by pruritus ani. Nausea, diarrhea, taste disturbance, flatulence, loose stool, and pruritus ani were significantly decreased in comparison with the previously reported groups. Only one case of mild aphthous ulcers (after tyrothricin troches) and no case of cheilosis was noted following the administration of troches in the presently reported study.

The incidence of mild gastrointestinal complaints in the placebo groups in this study again indicates that some of the reactions observed during these antibiotic troche tests may be the result of the taste masking bases in which antibiotics are incorporated. Impurities in antibiotic preparations have also frequently been reported as causing untoward reactions to therapy. Irritative excipients, binders, and impurities may therefore be instrumental in either producing or causing exacerbation of the reactions.

DISCUSSION

The antibiotics described in this study either have not been administered systemically (tyrothricin and gramicidin), or else have been administered systemically with the greatest care (bacitracin and polymixin B) owing to the severe characteristics of the reactions sometimes appearing following full systemic therapeutic dosage. Consequently, in preparing the oral troche dosage forms, sufficiently small amounts of these antibiotics may have been incorporated in the troche so as to obviate the possibility of systemic reactions resulting from

topical oral troche therapy. In so doing, however, it is possible that insufficient amounts of the antibiotic were incorporated in the troche in order to produce: (1) a therapeutically beneficial effect and (2) oral, gastrointestinal, and other reactions. It cannot be concluded from this study what reactions might be observed from bacitracin, tyrothricin, gramicidin, or polymixin B-bacitracin troche therapy if higher concentrations of the active antibiotics were administered, in which case side reactions and also therapeutic efficiency might both, perhaps, be increased.

Those gastrointestinal symptoms which were observed in the groups reported on in this article were felt to be due mainly to the continued ingestion of substances as nauseating to the taste of some individuals as bacitracin, tyrothricin, gramicidin, and polymixin B and also to the relatively continuous passage through the digestive tract of troche medicaments following slow dissolution in the oral cavity. As was noted in the previous articles all reactions were of necessity recorded; many, and especially those in the present study, should be considered as of extremely slight importance. If therapy of disease warrants antibiotic troche therapy with these specific agents in dosages as above, the reactions reported in this article to bacitracin, tyrothricin, gramicidin, or polymixin B could be weighed extremely lightly or ignored.

CONCLUSIONS AND SUMMARY

In a controlled study in which bacitracin troches were administered to 100 patients, tyrothricin troches were administered to 100 patients, gramicidin troches were administered to 50 patients, and polymixin B-bacitracin troches were administered to 100 patients, the resulting side reactions were evaluated. Of 100 patients receiving bacitracin medicated troches, 11 (11 per cent) evidenced untoward reactions compared with 5 (10 per cent) of the 50 patients who received placebo troches; of 100 patients receiving tyrothricin medicated troches, 12 (12 per cent) evidenced untoward reactions compared with 6 (12 per cent) of the 50 patients who received placebo troches; of 100 patients receiving polymixin B-bacitracin medicated troches, 9 (9 per cent) evidenced untoward reactions compared with 5 (10 per cent) of the 50 patients who received placebo troches; of 50 patients receiving gramicidin medicated troches, 4 (8 per cent) evidenced untoward reactions.

The reactions which occurred were of the mildest degree (with one exception) and did not require cessation of medication. They did not particularly affect the oral, pharyngeal, rectal, or anal areas. When compared with the results of previous studies with terramycin, aureomycin, and procaine penicillin G troches, the percentage of patients showing reactions, the average number of reactions per patient, and the average number of reactions per reactor were appreciably lower with bacitracin, tyrothricin, polymixin B, and gramicidin troches.

However, despite the minimal number and slight severity of reactions accompanying bacitracin, tyrothricin, gramicidin, and polymixin B-bacitracin troche medication, it is suggested that antibiotic medication with these agents be utilized only when their administration is specifically indicated and not for promiscuous use.

This study was carried out with the appreciated guidance and cooperation of Maurice J. Hickey, M.D., D.D.S., Associate Dean and Professor of Oral Surgery; Louis R. Stowe, D.D.S., Professor of Dentistry; Edward V. Zegarelli, D.D.S., Associate Professor of Dentistry; and Irvin L. Hunt, D.D.S., Associate Professor of Dentistry of the School of Dental and Oral Surgery of the Faculty of Medicine, Columbia University.

The authors also express their appreciation to the freshmen and sophomore classes of the Dental School for their cooperation and to Miss Mildred MacNeil for her assistance in coordinating the experimental procedures.

REFERENCES

1. Kutscher, A. H., Budowsky, J., Lane, S. L., and Chilton, N. W.: Reactions Following the Use of Terramycin Troches: A Controlled Study, J. ALLERGY **23**: 177, 1952.
2. Kutscher, A. H., Budowsky, J., Lane, S. L., and Chilton, N. W.: Reactions Following the Use of Aureomycin and Procaine Penicillin Troches: A Controlled Study, J. ALLERGY **24**: 164, 1953.
3. Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis With Special Reference to Side Effects, J. A. M. A. **142**: 161, 1949.
4. Williams, B., Jr.: Oral and Pharyngeal Complications of Chloramphenicol (Chloromycetin) Therapy, Am. Pract. & Digest. Treat. **1**: 897, 1950.
5. Woods, J. W., Manning, I. H., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**: 207, 1950.
6. Ellinger, P., and Shattock, F. M.: Nicotinamide Deficiency After Oral Administration of Penicillin, Brit. M. J. **2**: 611, 1946.
7. Goldman, L., and Farrington, J.: Stomatitis With Glossitis Following Oral Therapy With Penicillin Tablets, Arch. Dermat. & Syph. **57**: 399, 1948.
8. Beham, H., and Perr, H.: Stomatitis Due to Streptomycin, J. A. M. A. **138**: 495, 1948.
9. Kutscher, A. H., and Ziskin, D. E.: Folic Acid Treatment of a Case of Acute Gingival Hemorrhage, ORAL SURG., ORAL MED., AND ORAL PATH. **3**: 1400, 1950.
10. Plummer, N., and Wheeler, C.: The Toxicity of Sulfadiazine, A. J. M. Sc. **207**: 175, 1944.
11. Epstein, S.: Tyrothricin and Thrombin in Exodontia, J. Am. Dent. A. **38**: 599, 1949.
12. Harris, H. J.: Aureomycin and Chloromycetin in Brucellosis, Bull. New York Acad. Med. **25**: 458, 1949.
13. Queries and Minor Notes. Answer, J. A. M. A. **144**: 1225, 1950.
14. Summer, L. S., and Favour, C. B.: Biologic Complications of Penicillin Therapy, Am. J. M. Sc. **7**: 511, 1949.
15. Kutscher, A. H.: Oral Manifestations of Toxicity Following Antibacterial Therapy. A Review of the Literature With 5 Case Reports, New York State D. J. **17**: 261, 1951.
16. Kutscher, A. H., and Lane, S. L.: The Clinical Toxicity of Antibacterial Drugs. A Comparative Review of the Literature Based on 96,075 Cases Treated With the Sulfonamides and Antibiotics, ORAL SURG., ORAL MED., AND ORAL PATH. **5**: 347, 1952.
17. Kligman, A. M.: Are Fungus Infections Increasing as a Result of Antibiotic Therapy? J. A. M. A. **149**: 979, 1952.

630 WEST 168TH ST.

A NEW ALLERGY SYRINGE FOR TESTING AND TREATMENT

S. A. Axelrad, B.S.,* Woodmere, N. Y.

FOR many years the Cooke Allergy Syringe with asbestos packing has been used by the large majority of allergists throughout the world for intracutaneous testing and treatment.

The cost of the Cooke syringe as compared to the regular tuberculin syringe has probably been the determining factor in its wide use.

Objections to the asbestos packing were possible contamination, frequent replacement due to discoloration and unraveling, and the possibility of leakage of solutions behind the asbestos part of the plunger.

A new inorganic rubber known as Corsol has been developed after many years of experimentation. Corsol is nonabsorbent and has no effect on various extracts used by allergists, or other parenteral solutions used in general practice. Corsol is now available with the Cooke allergy syringe, replacing the asbestos cord.

Fig. 1 illustrates the Corsol packing, which is a tube on a threaded metal part.

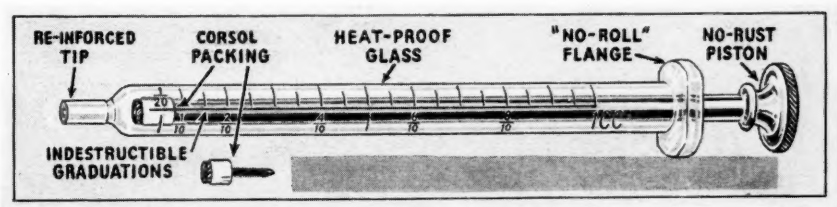


Fig. 1.

A *very slight turn* of the plunger in the barrel to the right tightens the seal, while a *very slight turn* to the left loosens the seal. This procedure is very important.

Corsol syringes have been tested for a very long time by many well-known allergists with excellent results, and can be sterilized in an autoclave up to 15 pounds pressure, or by wet sterilization to 220° F.

This syringe has great advantages over the asbestos type Cooke syringe and the all-glass tuberculin, because of the low cost and easy interchange of parts which will be available for replacement.

Received for publication Oct. 15, 1953.

*Formerly chemist to the Lederle Laboratories, New York, N. Y., and research chemist, United States Army, World War I.

SUMMARY

A new type Cooke syringe is described, consisting of the usual glass syringe barrel, with a chrome-plated nonrusting metal plunger, having the Corsol packing, as the seal between the plunger and the barrel. This new packing is nonabsorbent and is unaffected by allergen extracts, vaccines, other injectable medicaments, and by sterilizing temperatures. All parts are interchangeable and replaceable.

1040 Links Road.

Editorial

IT IS SO—IT AIN'T SO

CONTROVERSY rages around the clinical importance and frequency of food allergy in a more lively manner than around any other subject in the field of allergy. The reason for this undoubtedly lies in the difficulties which beset the clinician when he sets out by clinical experiment or observation to investigate it. Lacking the means to apply the necessarily rigid controls that are required in order to answer questions of this type there is a tendency either to apply inadequate controls and arrive at an unsupported answer or to take refuge in one's own clinical judgment, saying, in effect, that one simply "knows" that this or that *is* so. The unbelieving may likewise "know" that it *ain't* so or may even go so far as to set up an experiment of his own which "proves" the fallacy of the belief; more words, more papers, more heat—no answer.

One aspect of food allergy has been recently presented in this JOURNAL and elsewhere,[1, 2] namely, the prevention of major allergies in children of allergic families by the avoidance of cow's milk in the early months. There is no question that this is a highly desirable objective nor is the means, the substitution of soybean "milk" for cow's milk, although attended by a number of difficulties as described by Hill[3] on this page a short time ago, an entirely impractical approach. However, to the question, "Do the data as presented form a reliable basis for the conclusions reached?" we would answer with an unqualified "No."

Compare the form of this experiment with that regarded by well-qualified persons[4] as essential in studies of this kind. The authors selected 96 infants as the "experimental" group. The time over which the selection was made is not stated nor is it more than very questionably implied that these infants were to be subjects of a controlled study at the time they were selected. A second group comprising 65 infants, all siblings of infants in the experimental group, were likewise selected as controls. Again it is not stated when these were selected. The reader's fear that this group may have been heavily weighted with children who were brought to the author's attention precisely because they already had allergic disease is reinforced by the author's own doubts as to the suitability of this group for purposes of control and the selection by them of a second group.

The second or "nonrelated" control group of 175 subjects was selected from "the histories of 4,710 children in 1,215 allergic families." No mention is made of what measures were taken to insure a truly random sample. To choose 175 subjects from among so many must have involved careful scrutiny of each candidate, and it seems hardly conceivable that even with the utmost effort to avoid favoring the candidate as against the other, a truly random selection could be made. Furthermore, the two control groups appear to have

been selected from infants and children many of whom had or may have had allergic disease. These the authors compare with a group of children who, at the time they were selected, before or immediately after birth, could have exhibited *no* allergic manifestations. The application of tests of statistical significance to differences between the experimental and the two control groups as carried out by the authors is obviously irrelevant if the above criticisms are valid.

An experiment of this kind requires that the criteria for selection of subjects for the experiment, whatever group they are to fall into, be set up before the selection is made, and then rigidly adhered to.[4] Furthermore, some method is needed to insure that subjects fall into the experimental or the control group in such a way as to avoid conscious selection, a common means being the assigning of alternate cases to each of the groups. Had any attempt to do this been made in this study, it would have been mentioned by the author without any question.

It is perhaps pertinent that the authors overlooked an aspect of their data[2] which contradicts one of their conclusions.[1] Among those who developed major allergies (a group which may be regarded as homogeneous in this respect at least) the avoidance of cow's milk in the diet during infancy did *not* prevent the later appearance of sensitivity to cow's milk. Roughly 50 per cent of those developing major allergies in each of the three groups (50 per cent or 7 out of 14 of the "experimental" group; 50 per cent or 21 out of 42 of the "sibling" control group; and 55 per cent or 50 out of 91 of the "non-related" control group) developed allergy to cow's milk.[2] That the time of onset in the "experimental" group was later than in the other two was to be expected because in the first group cow's milk had been introduced later. This is evidence against the concept of immunologic immaturity as a temporary phenomenon associated with the first year or two of life. The absence of any mention of this point suggests preoccupation with one interpretation to the exclusion of all others. Did such an attitude play a part in the selection of the two control groups?

The above is not meant to imply that the authors consciously biased the results. Our quarrel stems from the apparent lack of any real attempt to avoid weighing the selection of subjects in one direction or another. In problems of this kind statisticians who, recognizing the pitfalls, would presumably be best qualified to afford themselves the luxury of dispensing with such precautions take great pains to randomize the selection of subjects because, among other things, they do not even trust themselves to do so without bias.

We selected this article for the above critical comment because the conclusions drawn are of great moment to everyone practicing allergy, especially preventive allergy. If the thesis is correct, it would virtually constitute malpractice to omit the steps they recommend in the feeding of infants born of allergic families. On the other hand, to follow the regimen recommended

without reasonable assurance of benefit would be hardly justified in view of the difficulties that beset the pediatrician and the mother when cow's milk is eliminated.

We feel the entire question remains open, and the answer will require an experiment planned well in advance with all precautions taken to avoid that enemy of science, human bias.

Francis C. Lowell and Irving W. Schiller.

REFERENCES

1. Johnstone, D. E., and Glaser, J.: Use of Soybean Milk as an Aid in Prophylaxis of Allergic Disease in Children, J. ALLERGY **24**: 434, 1953.
2. Glaser, J., and Johnstone, D. E.: Prophylaxis of Allergic Disease in the Newborn, J. A. M. A. **153**: 620, 1953.
3. Hill, L. W.: Editorial, J. ALLERGY **24**: 474, 1953.
4. Hill, A. B.: The Clinical Trial, New England J. Med. **247**: 114, 1952.

American Academy of Allergy

TENTH ANNUAL MEETING, SHAMROCK HOTEL, HOUSTON, TEXAS FEBRUARY 1, 2, AND 3, 1954

Postgraduate Courses and Scientific Program

A. Postgraduate Courses in Allergy (Preliminary Program), Jan. 29-31, 1954

COURSE 1. SPECIAL SUBJECTS IN CLINICAL ALLERGY

Friday, Jan. 29, 1954

10:00 A.M.—12:00. Registration—Shamrock Hotel.

Information concerning location of courses will be available at Registration Point at Shamrock Hotel.

2:00 P.M.—4:00 P.M. ACTH-Cortisone Symposium.

Panel discussion on physiologic and therapeutic considerations of ACTH-Cortone in allergic diseases.

Moderator: Dr. Bram Rose, Montreal, Canada.
Dr. William B. Sherman, New York, N. Y.
Dr. Francis Lowell, Boston, Mass.
Dr. Walter L. Winkenwerder, Baltimore, Md.
Dr. DeWitt Hotchkiss, Houston, Texas.

4:00 P.M.—5:30 P.M. Chronic Allergic Vasomotor Rhinitis including discussion of interrelationships of sinusitis and polyp formation. Panel discussion on etiology and therapy including surgical procedures.

Moderator: Dr. Walter L. Winkenwerder, Baltimore, Md.
Dr. Stanley Hampton, St. Louis, Mo.
Dr. Ben Rappaport, Chicago, Ill.
Dr. Lyle J. Logue, Professor of Clinical Otolaryngology, Baylor University, College of Medicine, Houston, Texas.

Saturday, Jan. 30, 1954

9:15 A.M.—12:00. Visiting Allergy Clinic.

Moderator: Dr. Harry L. Alexander, St. Louis, Mo.
Dr. Theodore L. Squier, Milwaukee, Wis.
Dr. Walter Burrage, Boston, Mass.
Dr. Edmund L. Keeney, San Diego, Calif.
Dr. DeWitt Hotchkiss, Houston, Texas.

Patients representing varied problems in diagnosis and therapy will be presented for discussion.

12:30 P.M. Luncheon, Shamrock Hotel. Guests of American Academy of Allergy.

Saturday, Jan. 30, 1954

2:00 P.M.—5:30 P.M. Symposium on Dermatologic Allergy

1. Atopic Dermatitis—Etiologic and Immunologic Considerations. Dr. A. Rostenberg, Professor of Dermatology, University of Illinois, College of Medicine.

2:00—2:30
Discussion 2:30—2:40

2. Weed Dermatitis—Incidence, Morphology, Therapy. Dr. J. B. Howell, Instructor in Dermatology, Southwestern Medical School, University of Texas.

2:40—3:10
Discussion 3:10—3:20

3. The Patch Test—Technique, Indications, Contraindications. Dr. J. Murray Riddell, Jr., Instructor in Dermatology, Southwestern Medical School, University of Texas.

3:20—3:50

Discussion 3:50—4:00

4. The Treatment of Allergic Dermatoses. Dr. Everett Seale, Professor of Dermatology, Baylor University, College of Medicine.

4:00—4:30

Discussion 4:30—4:40

5. "Information Please" Panel on Dermatologic Allergy. Dr. J. B. Howell, Dr. J. Murray Riddell, Jr., Dr. A. Rostenberg, Jr., Dr. Everett Seale.

4:40—5:30

COURSE 2. SEMINARS

(Afternoon of January 30 and morning of January 31)

These seminars are designed to keep advanced students informed of developments in applied and investigative phases of allergy. The subjects to be discussed are:

1. Histamine metabolism: biochemistry, synthesis, release, degradation; assay by biological, chemical, and tracer methods; physiologic action in relation to allergic states. Conducted by E. A. Zeller, Professor of Biochemistry, Northwestern University, and others.

2. Formed Blood Elements. The function of the various formed blood elements and their alteration in the allergic states. Conducted by William Dameshek, Director of the Blood Research Laboratory, New England Center Hospital, Boston, and others.

3. Species Patterns of Hypersensitiveness in Animals: Its Application to Human Allergy. A summary of the extensive studies of hypersensitiveness in various mammalian species correlated with their physiologic behavior. Significance of the differences in the interpretation of allergy in human beings. Course to be given by Drs. Samter, Saul Malkiel, and others.

COURSE 3. ALLERGENIC MOLDS AND POLLENS; IDENTIFICATION, DISTRIBUTION, CLINICAL SIGNIFICANCE

(January 29, 30, and morning of January 31)

The instruction in pollen recognition and in the standard technique of pollen counting will be under the supervision of Oren C. Durham. The instruction in recognition of fungus spores and fungi on gravity slides and culture plates will be supervised by Dr. Clyde M. Christensen, Professor of Mycology, University of Minnesota, and other well-qualified instructors.

The course, which will run concurrently with the preconvention clinical courses and seminars, is designed for technicians and physicians.

Fees:	Courses 1 and 2 combined	$50
	Course 2	15
	Course 3	35

Please send applications indicating course or courses selected to: Mr. A. Luthmers, American Academy of Allergy, 208 E. Wisconsin Ave., Milwaukee, Wis.

Checks should be made payable to the American Academy of Allergy.

B. Scientific Program (Preliminary), Feb. 1-3, 1954

MONDAY, FEBRUARY 1

Paper No.

1. A Study of Timed Vital Capacity and Forced Respiratory Curves in Patients With Pulmonary Disease. H. Beecher Chapin, Jean Roy, and Robert A. Cooke, New York, N. Y.

2. Clinical and Laboratory Estimation of the Severity of Bronchial Asthma. Francis C. Lowell, Irving W. Schiller, and Mary T. Lynch, Boston, Mass.

3. The Effect of Helium-Oxygen Mixtures on Pulmonary Function in Asthmatic and Emphysematous Patients. Irving W. Schiller, Francis C. Lowell, Mary T. Lynch, and William Franklin, Boston, Mass.
4. Maintenance Cortisone in Intractable Asthma: Preliminary Observations of Undesirable Cortisone Effects. John W. Irwin, Philip H. Henneman, David M. K. Wang, and Walter S. Burrage, Boston, Mass.
5. Prolonged Cortisone and Hydrocortisone Therapy. Carl E. Arbesman and Norman B. Richard, Buffalo, N. Y.

Intermission

6. Comparative Results of the Use of Hydrocortone, Cortisone, and ACTH in the Treatment of Intractable Bronchial Asthma and Pulmonary Emphysema. H. A. Bickerman and Alvan L. Barach, New York, N. Y.
7. The Use of Continuous Cortone Therapy in Elderly Asthmatics. Walter L. Winkenwerder, Baltimore, Md.
8. ACTH and Cortisone in the Treatment of Bronchial Asthma. Horace S. Baldwin, Paul F. de Gara, Aaron D. Spielman, and Murray Dworetzky, New York, N. Y.
9. The Excretion of Adrenocortical Steroids in Cases of Allergy. Bram Rose and E. H. Venning, Montreal, Canada.

Lunch

Guest Lecturer

2:00-3:00

The Development of Immunohematologic Concepts. William Dameshek, Director of the Blood Research Laboratory, New England Center Hospital, Boston, Mass.

Intermission

10. Effects of Histamine and Epinephrine on the Small Pulmonary Blood Vessels of Living Rabbits: An Experimental Study [Color Film]. Walter S. Burrage, John W. Irwin, and James I. Gallemore, Boston, Mass.
11. The Role of Adrenalin and a Monoamine Oxidase Inhibitor (Marsilid) in Anaphylaxis. Joseph Rebhun and Samuel M. Feinberg, Chicago, Ill.
12. Effect of Antitubercular Drugs on the Metabolism of Histamine and Sympathomimetic Amines. J. Barsky, E. R. Berman, J. R. Foute, and E. Albert Zeller, Chicago, Ill.
13. Release of Histamine in the Blood of Ragweed Sensitive Individuals. Joseph W. Noah and Alta Brand, St. Louis, Mo.
14. Comparison and Analysis of Lewis' Triple Response in Man Produced by (1) Histamine Phosphate and (2) a Histamine Liberator (Compound 48-80). Norman J. Ehrlich, Ruth Rhines, and Max Samter, Chicago, Ill.

TUESDAY, FEBRUARY 2

15. The Antigenic Relationship of the Pollen, Seed, and Leaves of Giant Ragweed. Samuel M. Feinberg, Joseph Rebhun, and Saul Malkiel, Chicago, Ill.
16. Studies on the Effect of Increasing the Concentration of Extraction on Yields of Allergenic Activity and Nitrogen Content. I. Timothy and Ragweed Pollen. Stanley F. Hampton, Mary C. Johnson, Sam Frankel, and Aline Schiele, St. Louis, Mo.
17. Chemical and Paper Chromatographic Investigation of Ragweed Pollen Extract. Sam Frankel, Mary C. Johnson, Aline Schiele, Samuel C. Bukantz, and Harry L. Alexander, St. Louis, Mo.

18. The Separation of Labeled Ragweed Antigen and Antiragweed Antibody. David W. Talmage, Chicago, Ill.

19. Complement Fixation Studies in Ragweed Allergy. Joseph Portnoy and William B. Sherman, New York, N. Y.

20. Immunochemical Studies of House Dust Allergen. Dan H. Campbell, Donald Z. Silver, and Wilton Vannier, Pasadena, Calif.

Intermission

21. Bronchial Asthma Unrelated to Positive Skin Reactions. Hyman Miller and Dorothy W. Baruch, Beverly Hills, Calif.

22. Skin Test Responses to Insulin and Serum Antihormonal Activity in a Case of Combined Insulin Allergy and Resistance. Samuel C. Bukantz and William G. Klingberg, St. Louis, Mo.

11:30 A.M. Dr. Murray Peshkin. Address by President, American College of Allergy.

Presidential Luncheon

President's Address. Ben Z. Rappaport

Guest Lecturer

2:00-3:00

The Dynamics of the Immune Response. Frank J. Dixon, Professor of Pathology, University of Pittsburgh, School of Medicine, Pittsburgh, Pa.

Intermission

23. Sensitivity to Digitalis (A Case Report). Milton M. Mosko, Chicago, Ill.

24. Passive Cellular Transfer of Neoarsphenamine Hypersensitivity in Guinea Pigs. A Oliveira Lima, Rio de Janeiro, Brazil.

25. Allergy to Foods Containing Sulfur-Amino-Acids; Case Report and Clinical Study. Louis Tuft, L. N. Ettelson, and Herbert Schwartz, Philadelphia. Pa.

26. Allergy and Immunization for Wasp Stings. Mary Hewitt Loveless, New York, N. Y.

Annual Business Meeting, 4:30 P.M.

WEDNESDAY, FEBRUARY 3

27. House Dust Allergy: I. Occurrence and Incidence of Seasonal Patterns of Asthma and Rhinitis. A. M. Targow, Los Angeles, Calif.

28. Further Studies on Biological Properties of Staphylococcus Extract. Murray Dworetzky, Horace S. Baldwin, Morton C. Kahn, and Marilyn K. Smart, New York, N. Y.

29. Haptene Aerosol Desensitization of Guinea Pigs Passively Sensitized to Specific Pneumococcus Polysaccharides. Oscar Swineford, Jr., Charlottesville, Va.

30. Studies on the Secondary Sensitization of Animals During Aerosol Induced Anaphylactic Shock in the Analysis of the Pathogenesis of Sensitization. Max Samter, Z. Z. Godlowski, and B. Z. Rappaport, Chicago, Ill.

Intermission

31. Tissue Cultures in Immunologic Studies of Hodgkin's Disease. Jack M. Rose and Jack R. Pulliam, Houston, Texas.

32. Allergic Dermatitis to Asparagus; A Case Presentation. Walter R. Kessler and James H. Barnard, New York, N. Y.

33. Topical Use of Hydrocortisone (Compound F) Ointment in Allergic Dermatoses. Sidney Friedlaender and Alex S. Friedlaender, Detroit, Mich.

34. Urticaria and Angioneurotic Edema: Statistical Survey of Five Hundred Cases. Milton J. Steinhardt, Detroit, Mich.

Abstracts of Papers to Be Presented

1. A STUDY OF TIMED VITAL CAPACITY AND FORCED RESPIRATORY CURVES IN PATIENTS WITH PULMONARY DISEASE

JEAN ROY, M.D., H. BEECHER CHAPIN, M.D., AND ROBERT A. COOKE, M.D.,
NEW YORK, N. Y.

(From the Institute of Allergy, Roosevelt Hospital)

Using the Vitalometer, described by Gaensler, the authors have done hundreds of determinations of timed vital capacity (before and after use of bronchodilator injections) on normal subjects and on patients suffering from chronic bronchial asthma. Their results are compared with similar work already published in medical literature.

The value and limitations of the previous method being recognized, the authors have substituted a rapidly moving kymograph to record the timed vital capacity during complete expiration and inspiration.

Data have been obtained on normal subjects, both male and female, in several age groups from 16 to 80 years of age. Patients with various types of pulmonary disease will be presented and the respiratory curves analyzed in relation to the established normal curves.

2. CLINICAL AND LABORATORY ESTIMATION OF THE SEVERITY OF BRONCHIAL ASTHMA

FRANCIS C. LOWELL, M.D., IRVING W. SCHILLER, M.D., AND
MARY T. LYNCH, M.D., BOSTON, MASS.

(From The Evans Memorial, The Massachusetts Memorial Hospitals, the Department of Medicine, Boston University School of Medicine)

The present study is an attempt to determine how reliable the estimation of the severity of bronchial asthma is when based on physician examination and statements made by the patient. The role played by other coexisting causes of respiratory symptoms, when present, was also included.

With this in mind, tests of pulmonary function were carried out in a group of asthmatic patients. Other tests involving the cardiovascular and other systems were included when indicated. In some instances patients were studied before and after measures designed to alter the severity of asthma.

The findings indicate that familiarity with the alterations in pulmonary physiology occurring in bronchial asthma is very helpful in the assessment of the asthmatic patient at the bedside. Examples of some of the problems encountered will be illustrated and discussed.

3. THE EFFECT OF HELIUM-OXYGEN MIXTURES ON PULMONARY FUNCTION IN ASTHMATIC AND EMPHYSEMATOUS PATIENTS

IRVING W. SCHILLER, M.D., FRANCIS C. LOWELL, M.D., MARY T. LYNCH, M.D., AND WILLIAM FRANKLIN, M.D., BOSTON, MASS.

(From The Evans Memorial, The Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine)

This study is an attempt to determine by measurement whether a mixture containing 80 per cent helium and 20 per cent oxygen, often recommended for alleviation of respiratory difficulty in bronchial asthma, can improve pulmonary function in asthmatic and emphysematous subjects.

Using a closed system which did not permit mixture of expired air with that to be inspired, patients with bronchial asthma, pulmonary emphysema, or both, were studied to determine the effect on pulmonary function of helium-oxygen mixtures. Minute volume, expiratory reserve volume, vital capacity, and rate of expiration with maximal effort were measured.

Arterial oxygen saturation was recorded by Millikan oximeter. The rate at which the blood became saturated in subjects rendered purposely hypoxic with either 10 per cent oxygen in nitrogen or 10 per cent oxygen in helium upon the administration of 100 per cent oxygen was also measured.

The results of these studies will be presented and their bearing on the use of helium-oxygen mixtures in asthmatic patients with severe respiratory distress will be discussed.

4. MAINTENANCE CORTISONE IN INTRACTABLE ASTHMA; PRELIMINARY OBSERVATIONS OF UNDESIRABLE CORTISONE EFFECTS*

JOHN W. IRWIN, M.D., PHILIP H. HENNEMAN, M.D., DAVID M. K. WANG, M.D., AND WALTER S. BURRAGE, M.D., BOSTON, MASS.

(From the Medical Service of the Massachusetts General Hospital and the Department of Medicine, Harvard University)

Patients with constant, intractable, perennial asthma of unknown etiology often present perplexing therapeutic problems. Some become refractory to many modes of treatment and rapidly progress to chronic invalidism. Over thirty of these patients have been maintained essentially symptom-free on daily doses of cortisone during the past three years. Weekly or bimonthly physical examinations, frequent laboratory studies, and detailed investigation of every complaint have been made.

It is our clinical impression that sufficient cortisone must be given initially to free the patient of asthma and that maintenance dosage does not depend on body mass or severity of the original symptoms.

Certain complications such as gastrointestinal bleeding, hypertension, hyperglycemia, symptomatic potassium deficiency, overwhelming infection, menstrual changes, psychosis, and symptomatic metabolic alkalosis have been absent to date. Mild obesity, acne, facial rounding, and hirsutism in females have been noted in some patients.

Under investigation and of present concern in this entire group is the effect of cortisone on maintenance of bone growth. Studies in a single case demonstrate rapidly progressive osteoporosis with multiple vertebral fractures and characteristic hypercalcuria.

*Supported by the Allergy Clinic Fund of the Massachusetts General Hospital. Cortisone used in this study was, in part, supplied through the courtesy of Merck and Co., Inc.

5. PROLONGED CORTISONE AND HYDROCORTISONE THERAPY

CARL E. ARBESMAN, M.D., AND NORMAN B. RICHARD, M.D., BUFFALO, N. Y.

(From the Buffalo General and Children's Hospitals of the University of Buffalo School of Medicine)

Only those patients with bronchial asthma, allergic rhinitis, urticaria, and so forth, who failed to respond to the usually accepted therapeutic measures, were treated with either cortisone or hydrocortisone.

A total of seventy-four such patients had oral cortisone therapy for periods of from one week to over three years. (Twenty-five of these patients had had ACTH therapy.) Thirty-six patients received cortisone for more than two months. Twenty-seven patients received hydrocortisone in place of cortisone at different times during the period of observation. (Nineteen of these twenty-six patients had had ACTH therapy at one time.) Hydrocortisone was used for over two months by twelve patients. The age of those treated varied from five to seventy-four years, and duration of previous symptoms from one month to sixty years.

The clinical response to each of these steroids in bronchial asthma, allergic rhinitis, nasal polyps, and chronic urticaria was studied. Likewise, the comparative effectiveness and dosage of cortisone and hydrocortisone in the same patient at different times is reported. The side effects of the two steroids are included in this survey.

Nine patients with bronchial asthma and aspirin sensitivity incorporated in the above groups are described as a special group.

The advantages and limitations, as well as maintenance therapy of cortisone and hydrocortisone, are described.

6. COMPARATIVE RESULTS OF THE USE OF HYDROCORTONE, CORTISONE, AND ACTH IN THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

H. A. BICKERMAN, M.D., AND ALVAN L. BARACH, M.D., NEW YORK, N. Y.

(From the Department of Medicine, College of Physicians and Surgeons, Columbia University, the Presbyterian Hospital, and the Columbian Division, Goldwater Memorial Hospital)

A clinical study is presented of the results of a standard dosage program of ACTH, cortisone, and hydrocortone in the treatment of 150 patients with intractable bronchial asthma or the bronchospastic type of emphysema. With the use of a five-day regimen of ACTH, clinical improvement began on the first or second day of treatment as contrasted to the fifth or sixth day of treatment with the employment of cortisone administered in a ten-day course. The length of the remission in the severe chronically recurring case of bronchospastic disease was two weeks with each drug. Longer remissions occurred in the patient whose disease had been previously under moderate control with bronchospasm appearing as a result of respiratory infection, and in patients with pollen allergy.

The response to hydrocortone was found to be sharply different from that to cortisone in that improvement took place on one-half the dosage of cortisone, with an onset of benefit on the first or second day of treatment. The side effects of the use of hydrocortone were correspondingly less. Our preliminary impression is that hydrocortone is the preferred method of treatment because of the early initiation of therapeutic response in the presence of a smaller dosage requirement.

7. ACTH AND CORTISONE IN THE TREATMENT OF BRONCHIAL ASTHMA

HORACE S. BALDWIN, M.D., PAUL F. DEGARA, M.D., AARON D. SPIELMAN, M.D., AND MURRAY DWORETZKY, M.D., NEW YORK, N. Y.

Clinical experience using ACTH and cortisone in the relief of acute episodes of asthma and in chronic intractable asthma from June, 1950, to June, 1953, is described. Sixty cases comprise the series of patients seen at the New York Hospital and in private practice. Twenty-five cases of intractable asthma require ACTH or cortisone most of the time. Of the series five have died. The largest amount of the hormones used in a single patient over this three-year period was 62.3 Gm. of cortisone and 7.7 Gm. of ACTH. Experiences with hydrocortone are also described. In several cases cortisone and ACTH were used alternately. The usefulness of respiratory function tests and the Thorne test in guiding therapy is summarized. Over-all management of the patient with bronchial asthma is emphasized, but it is apparent that with proper precautions ACTH and cortisone may be used to relieve acute attacks and in certain cases over long periods of time with important clinical relief to the asthmatic state.

8. THE EXCRETION OF ADRENOCORTICAL STEROIDS IN CASES OF ALLERGY

BRAM ROSE, M.D., AND E. H. VENNING, M.D., MONTREAL, QUEBEC, CANADA

(From the McGill University Clinic, Royal Victoria Hospital)

During the past four years observations have been made on a series of 70 patients, the majority cases of asthma, and the remainder atopic dermatitis or urticaria. The glucocorticoids and 17-ketosteroids of the urine were measured before, during, and after the administration of ACTH, cortisone, or hydrocortisone, and the results compared with the clinical course of the patients, eosinophile counts, and other pertinent data. In addition to this form of therapy similar observations were made on a patient treated with artificially induced fever, as well as nonspecific therapy during hospitalization with spontaneous remission. Some of these patients have had assessment of steroid excretion three to four times during the course of this period of time.

In reviewing the results it appears that there is a decline of corticosteroid output in the urine of the older group of asthmatics which is lower than that observed for a group of controls of the same age group. Generally, the administration of ACTH causes an increase in the level of corticosteroids but this is usually at the higher level of normal and sometimes a little above. In contrast, the younger group show a normal excretory output of corticosteroids during asthma, and a marked increase to well above normal following stimulation by ACTH. It has not been possible to relate the level of the corticoid output to severity of the disease process in the asthma except in cases undergoing spontaneous remission in the hospital. Here, a definite but small increase in the level of the urinary corticosteroids can be seen as the symptoms disappear. Similar findings have been observed in a single case of asthma and atopic dermatitis treated in the hospital by intravenous typhoid vaccine with the production of fever.

Compared to the cases of asthma, a high level of urinary corticosteroids has been found in cases of both atopic dermatitis and urticaria. Many of the latter showed an eosinopenia as well and did not respond to either ACTH or cortisone therapy. Since the glucocorticoids are biologically assayed in terms

of active compound E and are thought to measure this type of activity, it is possible that there is a degree of adrenocortical suppression during asthma in the older patient. It is very likely, however, that acute and chronic asthma are unable as disease entities to stimulate the pituitary adrenal mechanism as shown by the above results.

9. URINARY EXCRETION OF HISTAMINE IN PATIENTS WITH ASTHMA AND HAY FEVER WITH OBSERVATIONS ON CHANGES PRODUCED BY ADMINISTRATION OF CORTISONE

Ross G. Mitchell, M.D., George B. Logan, M.D., Gustovus A. Peters, M.D., and Lowell L. Henderson, M.D., Rochester, Minn.

(From the Mayo Clinic)

A study has been made of the urinary excretion of histamine by children and adults between allergic attacks, during allergic attacks, and during attacks treated by the administration of cortisone.

Urine was collected for periods of twenty-four hours. The urinary content of both free and conjugated histamine was determined by the method of Roberts and Adam.

Fourteen children were studied in quiescent periods. Ten children were studied during acute attacks. Four adults and two children were studied during acute attacks in which cortisone was given.

It was found that these fourteen children excreted normal amounts of free and conjugated histamine in the urine in the intervals between allergic attacks. During acute attacks, the excretion of free histamine tended to be low, suggesting that free histamine may be retained in the body.

The administration of adrenocortical hormones to patients who had acute attacks of allergy resulted in an increased elimination of free histamine in the urine, which may be abnormally great in cases of severe degree. The effect of these hormones on conjugated histamine was variable.

10. EFFECTS OF HISTAMINE AND EPINEPHRINE ON THE SMALL PULMONARY BLOOD VESSELS OF LIVING RABBITS: AN EXPERIMENTAL STUDY*

Walter S. Burrage, M.D., and John W. Irwin, M.D., Boston, Mass., and James I. Gallemore, Charleston, S. C.

With the Technical Assistance of Priscilla Gordon and Mary J. Graham

(From the Medical Service of the Massachusetts General Hospital and the Department of Medicine, Harvard University)

Intratracheal oxygen, delivered under pressure, has made it possible to stop all respiratory movements in living anesthetized rabbits, thereby permitting direct microscopic observation of an exposed lobe of the right lung. Knisley's quartz rod method of transillumination provided light for this study of small living pulmonary blood vessels. Pulmonary arterioles varying in diameter from 150 micra to 10 micra, capillaries from 5 to 20 micra, and venules from 10 to 160 micra were studied microscopically before, during, and after the intravenous injection of various doses of histamine and epinephrine.

Observed changes were divided into two groups: effects on the walls of the various pulmonary vessels and effects on the intravascular elements. The

*Supported by Allergy Clinic Fund of the Massachusetts General Hospital and the Mary Dexter Fund.

dominant effects of epinephrine appeared to be dilatation of the pulmonary arterioles, capillaries, and venules with a marked increase in the rate of linear blood flow. The main changes noted after histamine were the formation of thrombi in venules and arterioles, marked dilatation of the capillaries, and the loss of blood cells through the walls of capillaries, end venules, and end arterioles. These and other effects will be demonstrated by a 16 mm. colored motion picture film.

11. THE ROLE OF ADRENALIN AND A MONOAMINE OXIDASE INHIBITOR (MARSILID) IN ANAPHYLAXIS

SAMUEL M. FEINBERG, M.D., AND JOSEPH REBHUN, M.D., CHICAGO, ILL.

(From the Department of Medicine, Northwestern University Medical School)

Since Marsilid has been shown to inhibit the action of monoamine oxidase which destroys adrenaline, it was thought that this drug might be useful in the treatment of allergy by augmenting the endogenous adrenaline. To test this possibility, experimental procedures were devised whereby the effect of Marsilid on endogenous and exogenous adrenaline was tested by its influence on anaphylaxis in guinea pigs. Since there has been disagreement as to the quantitative and temporal factors concerned in the effect of adrenaline in anaphylactic shock, experiments were set up to obtain data on these questions. Our observations show that there is a narrow range between the toxic dose of adrenaline administered in single doses and the amount required for protection against anaphylactic shock or asthma from an aerosolized antigen. By infusion the tolerated dose gave better protection. Marsilid failed to produce protection against these anaphylactic procedures. It can be inferred that the partial inhibition of the degradation of the adrenaline attributed to the action of Marsilid is insufficient to affect the endogenous adrenaline which might control anaphylaxis in the guinea pig.

12. EFFECT OF ANTITUBERCULAR DRUGS ON THE METABOLISM OF HISTAMINE AND SYMPATHICOMIMETIC AMINES

E. A. ZELLER, PH.D., M.D., J. BARSKY, M.A., E. R. BERMAN, M.S., AND J. R. FOUTS, B.A., CHICAGO, ILL
(BY INVITATION)

(From the Department of Biochemistry, Northwestern University Medical School)

The new antitubercular drugs, isoniazid and iproniazid, produce, among the side reactions, asthma and disturbances of the autonomic nervous system. In connection with our studies on the action of basic antibodies and basic antitubercular substances on bacterial enzymes (J. Biol. Chem., vol. 192, 1951), we investigated the influence of the new drugs on mammalian diamine oxidase = histaminase (DO) and monoamine oxidase (MO). In addition, a product of low toxicity, pyruvic acid isonicotinoyl hydrazone, Eli Lilly (PIH) was tested. It was found that, on comparing various species and various drugs, there was a parallelism between the toxicity of the compounds and the action on MO and DO. Iproniazid, the most toxic drug, is a most powerful inhibitor of MO, while isoniazid is a moderate inhibitor of MO and DO. PIH hardly affects these enzymes. With iproniazid the MO of 4 species has been blocked completely in vivo. Since MO inactivates epinephrine and other sympathicomimetrically active amines, the response toward these compounds should be different in an iproniazid-treated animal as compared with the control. This is true, as has been shown by the work of Griesmer and associates and Rebhun and associates (unpublished data).

Thus it can be concluded that some of the side reactions produced by these drugs are caused by their action on MO and DO. With this information, it will be possible to interpret more precisely the symptoms of side reactions and to develop new derivatives which are less toxic.

13. RELEASE OF HISTAMINE IN THE BLOOD OF RAGWEED-SENSITIVE INDIVIDUALS

JOSEPH W. NOAH, M.D., AND ALTA BRAND, ST. LOUIS, MO.

(From the Department of Internal Medicine, Washington University School of Medicine)

A microchemical technique of histamine assay has been employed in determining the amount of histamine released when the blood of ragweed-sensitive individuals is exposed to ragweed antigen.

The method described by Lowry, Graham, and Harris, a specific determination based on the spectrophotometric observation of the compound of histamine with dinitrofluorobenzene, was applied to plasma samples obtained after centrifugation of whole blood incubated with ragweed antigen for twenty minutes at 37° C. Blood was taken from individuals whose sensitivity to ragweed was well established on the basis of unquestionable seasonal incidence and significant skin test reactions.

The results obtained confirm those reported by Katz in 1941. A greater release of histamine was obtained than that previously reported, however, averaging 900 per cent of normal values in 11 individuals, and in one individual reaching 2,500 per cent of normal; i.e., the value of histamine in plasma samples not exposed to antigen. Blood of five subjects not ragweed sensitive showed no significant increase in plasma histamine values with this procedure.

The possible source of the histamine released into the plasma will be discussed with reference to distribution of histamine among the various blood elements as found by Graham, Wheelwright, Parish, Marks, and Lowry. Possible clinical significance of the phenomenon of histamine release will be considered.

14. COMPARISON AND ANALYSIS OF LEWIS' TRIPLE RESPONSE IN MAN PRODUCED BY (1) HISTAMINE PHOSPHATE AND (2) A HISTAMINE LIBERATOR (COMPOUND 48-80)

NORMAN J. EHRLICH, M.D., RUTH RHINES, M.D., AND MAX SAMTER, M.D., CHICAGO, ILL.

(From the Department of Medicine and the Allergy Unit, University of Illinois College of Medicine)

Skin reactions were produced in seventy-two persons—normal subjects, allergic individuals, and patients suffering from various diseases—by the intradermal injection of solutions of histamine phosphate and of Compound 48-80, a potent histamine liberator, prepared for us by Dr. de Beer of The Wellcome Research Laboratories.

Our findings indicate:

1. That individuals differ widely in their response to the injection of histamine phosphate and Compound 48-80.

2. That each individual, however, shows approximately the same response to the injection of Compound 48-80 as to the introduction of exogenous histamine phosphate.

In an attempt to elucidate the phenomenon of the identical response to endogenous and exogenous histamine we repeated the study after altering the vascular phase of the triple response by pretreatment with sympatholytic drugs. The results are reported and reviewed in the light of the existing experimental evidence on the action of Compound 48-80 and other histamine liberators such as dextran and PVP.

15. THE ANTIGENIC RELATIONSHIP OF THE POLLEN, SEED, AND LEAVES OF GIANT RAGWEED

JOSEPH REBHUN, M.D., SAUL MALKIEL, M.D., AND SAMUEL M. FEINBERG, M.D., CHICAGO, ILL.

(From the Department of Medicine, Northwestern University Medical School)

This report deals with studies on the antigenic relationship of the pollen, seed, and leaves of giant ragweed. The purpose of these investigations was to shed light on (1) the possibility that plant debris of the ragweed may serve as a cause of allergic symptoms after the pollinating season; (2) the plant extract might serve as a substitute for the pollen in the preparation of antigens for diagnosis and therapy; and (3) for the procurement of basic immunologic information on the general problem of organ specificity.

After preliminary testing with crude extracts purified fractions were prepared by several methods from the pollen, seed, and leaves. The preparations of each organ were compared with the preparations of the other organs by means of direct skin tests in ragweed-sensitive patients, cross testing of sites passively sensitized with reaginic serum, anaphylaxis in the guinea pig and precipitin test. The results indicate that the pollen antigen is present in the seed and leaves, but in greatly reduced quantities. The antigenic relationship is closest between the leaf and the pollen antigen. It is doubtful that the ragweed plant contains a sufficient proportion of antigen to serve as a practical source of the preparation for diagnostic or therapeutic extracts. However, the results suggest that it is possible that the plant debris may constitute a source of allergen to the pollen-sensitive patients.

16. STUDIES ON THE EFFECT OF INCREASING THE CONCENTRATION OF EXTRACTION ON YIELDS OF ALLERGENIC ACTIVITY AND NITROGEN CONTENT. I. TIMOTHY AND RAGWEED POLLEN

STANLEY F. HAMPTON, M.D., MARY C. JOHNSON, A.B., SAM FRANKEL, M.A., AND ALINE W. SCHIELE, A.B., ST. LOUIS, MO.

(From the Department of Medicine, Washington University School of Medicine)

The relationship between concentration of extraction of dried, defatted hay fever producing pollens and the yield of allergens has been the subject of a number of reports. Some studies have been oriented toward determining the weight by volume ratios which would provide the optimal yield of allergens. As part of an attempt to isolate essential pollen antigens and because the results of these earlier reports have been contradictory, it was felt desirable to repeat the analyses by performing neutralization tests on a number of extracts derived from increasingly concentrated mixtures of pollen and extracting fluid. The allergenic yield was compared with the nitrogen and carbohydrate content of the final extracts.

Several lots of timothy and low ragweed pollen were extracted with both buffered saline (S) and 50 per cent glycerinated buffered saline (G) at seven different weight by volume ratios, varying from 1 to 50 per cent. There was direct linear relationship, over the entire concentration range, between allergenic yield measured by reagin neutralization tests, the total and phospho-

tungstic acid precipitable (PTA) nitrogen, and total carbohydrate content. The PTA nitrogen concentration of 40 per cent extracts was 900 per cent greater than that of 5 per cent although there was a loss of 35 per cent of the total recovered PTA nitrogen.

The highly concentrated G extracts have maintained reagin neutralizing activity and have remained clear for one year while S extracts of comparable concentration have sedimented heavily within two weeks.

Direct yield of such potent and stable extracts eliminates need for concentrating procedures and is useful both clinically and experimentally, particularly where incorporation of highly concentrated extracts with adjuvants in small volume is desired.

17. CHEMICAL AND PAPER CHROMATOGRAPHIC INVESTIGATION OF RAGWEED POLLEN EXTRACT*

SAM FRANKEL, M.A., MARY C. JOHNSON, B.A., ALINE SCHIELE, B.A., SAMUEL C. BUKANTZ, M.D., AND HARRY L. ALEXANDER, M.D., ST. LOUIS, MO.

(From the Department of Internal Medicine, Washington University School of Medicine)

An investigation of ragweed pollen extract by chemical and paper chromatographic methods for the purpose of isolating the smallest possible active component yielded the following information:

1. In agreement with Rockwell, the smallest active component consisted of a polypeptide-carbohydrate-pigment complex. However, rather than the monomolecular pentose which Rockwell described, evidence indicates that the carbohydrate component exists as a polysaccharide composed entirely of arabinose. Other carbohydrate components present in the extract were free glucose and fructose. Several fractionation procedures failed to produce an active fraction that was entirely free of either nitrogen or carbohydrate. Carbohydrate-free fractions obtained were 10.4 per cent nitrogen, but the method of isolation was fatal to the activity. A fraction containing 74.4 per cent bound arabinose and only 1.5 per cent nitrogen was obtained by mild alkaline hydrolysis and retained approximately one-half of the original activity as determined by skin tests.

2. The solvent used for the separation of a mixture of biologically active materials by filter paper chromatography must be chosen with great care. Lutidine, used for the separation of components in dialyzed ragweed extract by Dankner and associates, can combine chemically with certain of the fractions and is in itself capable of producing positive skin tests. However, the fact that those fractions were truly biologically active was confirmed by isolating similar fractions using the nonskin reacting solvent, methyl cellosolve.

3. Successive degradation of the fractions upon further treatment for the purpose of purification suggests the possibility that the biological activity found in the dialyzable portion of ragweed extract is due to the presence of breakdown products from originally nondialyzable materials.

18. THE SEPARATION OF LABELED RAGWEED ANTIGEN AND ANTIRAGWEED ANTIBODY

DAVID W. TALMAGE, M.D., CHICAGO, ILL.

C_{14}-labeled ragweed and I^{131}-labeled antiserum from ragweed-sensitive human beings have a high potential usefulness in studies of reaction between antigen and skin-sensitizing antibody. Before either labeled antigen or labeled antibody can be used in immunologic studies they must be separated from the overwhelming background of nonspecific radioactivity.

*Aided by a grant from the Lasdon Foundation, Nepera Park, Yonkers, N. Y.

Various methods of separation have been tried, all with the following two steps in common:

1. A specific precipitation or absorption of the labeled antigen or antibody.
2. Elution of the labeled antigen or antibody by exchange with excess carrier.

Insoluble pollen residues, tannic acid precipitates of ragweed extract, and immune precipitates from ragweed extract and rabbit antiserum have been used as absorbents for labeled antibodies.

Labeled antigen has been precipitated with specific rabbit antiserum and the antigen in the precipitate eluted with excess unlabeled ragweed extract. The success of separation procedures is determined by the degree of reaction between labeled antigen so obtained and its homologous antibody. To date, antigen mixtures with 25 per cent isotopic specificity have been obtained, which represents considerable purification. Further concentration is desirable and studies to that end are in progress after which the labeled antigen can be used in immunologic studies.

19. COMPLEMENT FIXATION STUDIES IN RAGWEED ALLERGY

JOSEPH PORTNOY, M.D., AND WILLIAM B. SHERMAN, M.D., NEW YORK, N. Y.

Studies of the antibodies concerned in allergic disease have been hampered by the lack of suitable in vitro methods for their demonstration. In vivo methods, currently employed, are subject to difficulties in performance and interpretation, and are far from being reproducible.

In this report, certain studies concerned with the development of a complement fixation inhibition reaction for blocking antibodies found in human sera treated with ragweed extracts and the comparative results obtained with this reaction and the passive transfer test will be presented.

It will be shown that the direct complement fixation reaction, using glycerin-preserved antigens, is a sensitive tool detecting as little as 0.05 μg of antigen protein N. This reaction may therefore prove to be of value in the purification and standardization of ragweed extracts.

Further, the complement fixation inhibition reaction, although less sensitive than the passive transfer technique for blocking antibody against ragweed antigen, appears to be specific, reproducible, and is correlated with the in vivo method. Sera giving a reaction of 500 units or more in the passive transfer test were positive in the complement fixation inhibition test.

These findings suggest that the complement fixation inhibition test may be of value as a screening method to determine the presence of antibodies in ragweed-treated cases and in other studies of the immunology of pollinosis. Further, this method may find application in the study of other allergens and their respective antibodies.

20. IMMUNOCHEMICAL STUDIES OF HOUSE DUST ALLERGEN

DAN H. CAMPBELL, PH.D., DONALD Z. SILVER, PH.D., AND
WILTON VANNIER, M.D., PASADENA, CALIF.

(From the Division of Chemistry and Chemical Engineering, California Institute of Technology)

The investigation of house dust in an effort to find a characteristic antigen has been made during the past four years under the sponsorship of the Academy of Allergy. During this period many different extraction methods were used and preparations were obtained from a large pool of house dust and of mattress dust. The final products were essentially the same in all cases. The skin-reactive antigen which seems to be common to dusts studied

so far is a polysaccharide containing galactose, rhamnose, xylose, mannose, and an amino sugar not yet identified. It is ash-free, slightly colored, and has a molecular weight of 10,000 to 15,000. It is homogeneous in the analytical centrifuge but shows two electrophoretic components at pH 4.0. The main component is colorless and is slightly more acidic than acetic acid. Clinical tests by various members of the Academy are still underway. The results so far indicate that this substance has the same order of test antigenicity as standard preparations. The total number of positive skin tests may be smaller but clinical cases of sensitivity to house dust usually give strong positive reactions.

21. BRONCHIAL ASTHMA UNRELATED TO POSITIVE SKIN REACTIONS

HYMAN MILLER, M.D., AND DOROTHY W. BARUCH, PH.D., BEVERLY HILLS, CALIF.

A boy of 3 having recurrent attacks of bronchial asthma was found to have numerous positive skin reactions to foods and inhalant allergens. The patient presented several disturbing paradoxes which commonly confront allergists: (1) his attacks were intermittent despite continuous exposure to the positively reacting inhalants, and (2) the attacks recurred despite omission of positively reacting foods from the diet. Furthermore, asthma failed to develop on many occasions when such foods were included in the diet. Careful control of the possible allergic and infectious factors had not prevented the recurrence of asthma.

Play psychotherapy with the child and psychoanalytically oriented therapy with each parent were then instituted. The data from all three sources will be presented in a manner which it is believed makes it possible to indicate that the emotional interplay between these three individuals was responsible for either setting off or, at times, aborting attacks of asthma in the child, regardless of the time or degree of his exposure to the reacting allergens. This suggests that, in this case at least, the positively reacting allergens had little if anything to do with the production of clinical symptoms. The thesis is developed that (1) the positive skin reactions may represent an immunologic response to previous exposure to the antigens, and that (2) such patients as these may express emotional problems somatically in some form recognized as clinical allergy quite independently of immunologic responsiveness.

22. SKIN TEST RESPONSES TO INSULIN AND SERUM ANTIHORMONAL ACTIVITY IN A CASE OF COMBINED INSULIN ALLERGY AND RESISTANCE*

SAMUEL C. BUKANTZ, M.D., AND WILLIAM G. KLINGBERG, M.D., ST. LOUIS, MO.

(From the Department of Medicine and the Department of Pediatrics, Washington University School of Medicine)

A 3½-year-old male diabetic child was admitted to the St. Louis Children's Hospital in moderate acidosis. Controlled with 12 units of regular and 6 units of protamine zinc insulin prior to his admission, he exhibited considerable insulin resistance during hospitalization and could not be regulated with 350 to 430 units of regular insulin daily. Concurrently he exhibited marked local reactions at injection sites, conjunctival reddening and nasal congestion following injections, and a blood eosinophilia of 17 per cent.

Direct intradermal skin tests were performed with 0.02 ml. of a number of insulin preparations. Beef, pork, and mixed crystalline insulins provoked wheal and erythema reactions while control normal and nonallergic diabetic

*Insulin preparations were generously supplied by Eli Lilly & Company.

subjects yielded no reactions. Because positive skin tests were also obtained with beef but not with pork muscle extract, it seemed evident that the patient was reacting to the insulin preparations.

Aged neutralized commercial insulin yielded a positive skin test while trypsin-digested insulin (free of hyperglycemic factor) yielded negative skin tests. A solution of hyperglycemic factor, alone, at 25 α/cc concentration, yielded a positive skin test comparable to that of crystalline insulin. Exposure of commercial insulin to boiling water for 30 to 180 minutes had no effect upon the skin reactive material. Treatment of the child with trypsin-digested insulin for twenty-four hours had no greater effect on reducing blood sugar than had commercial insulin.

Serum from the patient and control subjects exhibited antihormonal properties in mouse convulsion tests.

The observations suggest that (1) allergy to insulin was directed against a contaminant rather than the hormone, (2) the allergen in insulin is heat stable, and (3) serum from normal as well as diabetic patients may exhibit anti-insulin properties in mouse convulsion tests.

23. SENSITIVITY TO DIGITALIS (A CASE REPORT)

MILTON M. MOSKO, M.D., CHICAGO, ILL.

(From the Department of Medicine and the Allergy Unit, University of Illinois College of Medicine)

Since the reference by Morrow in 1887 to three cases of digitalis sensitivity there have been very few references of allergy to this commonly used drug. The few cases cited demonstrated urticaria, and none demonstrated skin-sensitizing antibody.

This case report is of a 53-year-old Negro man, who had been treated with tincture of digitalis for two months. The drug was then discontinued for two weeks, and then two days after readministration the patient developed severe angioedema and large bullae of both arms. After five days there was subsidence interrupted only by occasional episodes of generalized urticaria.

Because of signs of congestive heart failure he was started on Digitoxin. In three days he developed severe angioedema which by the twelfth day was generalized and associated with large bullae. All medication was stopped and all symptoms abated and were gone by the fifth day.

On two subsequent occasions Digitoxin therapy was followed in three days by a recurrence of angioedema and large blebs. This also occurred several times after skin testing to digitalis preparations.

Direct immediate skin reactions were elicited for Digitoxin, Lantocide C, and Digilanid. The passive transfer test was positive for Digitoxin, as was the test with Digitoxin. Passive transfer from aspirated bullous fluid gave positive reactions for Digitoxin and Lantocide C.

24. PASSIVE CELLULAR TRANSFER OF NEOARSPHENAMINE HYPERSENSITIVITY IN GUINEA PIGS

A. OLIVERIA LIMA, M.D., RIO DE JANEIRO, BRAZIL

(From the Allergy Section, Department of Dermatology, National School of Medicine)

From the results so far obtained with homologous cellular transfer of specific sensitivity to bacterial products and chemical compounds, it would appear that three types of sensitivity are amenable to passive transfer, in animals and human beings: (1) the delayed tuberculin type, (2) the anaphylactic type, and (3) the wheal and erythema type. It has not been possible to demonstrate unequivocally the passive transfer of the delayed eczematous contact type of sensitivity in human beings.

This investigation was designed to test the hypothesis of cellular transfer of the dermal (delayed) neoarsphenamine hypersensitivity in the guinea pig. The packed peritoneal cells obtained from 10 animals with high dermal sensitivity to neoarsphenamine were polled and resuspended in about 14 ml. of Tyrode's solution containing 10 per cent normal guinea pig serum. About 0.2 ml. of this suspension containing approximately 0.15 ml. of viable cells was injected intraperitoneally into each of 8 normal recipients. Four normal animals received, as control, about 0.2 ml. of pooled peritoneal cells similarly obtained from 5 nonsensitized guinea pigs. The recipient animals (sensitized and control) were tested for skin sensitivity forty-eight or seventy-two hours after cell transfer, by intradermal injections of 0.15 mg. of neoarsphenamine in 0.1 ml. saline.

The results of this investigation showed unequivocally that the peritoneal cells from sensitized guinea pigs were able to induce a specific dermal sensitivity to the whole skin of homologous nonsensitized recipients.

25. ALLERGY TO FOODS CONTAINING SULFUR-AMINO-ACIDS: CASE REPORT AND CLINICAL STUDY

LOUIS TUFT, M.D., L. N. ETTELSON, M.D., AND HERBERT SCHWARTZ, B.S., PHILADELPHIA, PA.

(From The Veterans Administration Regional Office and Temple University Allergy Clinic)

A clinical study was carried out upon a 27-year-old atopic male chemist with recurrent urticaria and nasal and cerebral symptoms of allergy. The latter had been attributed since childhood to "sinusitis" but, despite negative intracutaneous skin reactions, were proved by diet trial to be due to allergy to certain foods, including egg, garlic, and molded cheeses. Thus on repeated occasion ingestion of egg would be followed by nasal and cerebral symptoms lasting varying lengths of time according to the amount eaten. Since egg is high in content of sulfur-containing amino acids, notably methionine and cystine, and because repeated and deliberate inhalation of H_2S fumes seemed to induce similar reaction, the possibility of an allergy to these amino acids was suggested. Because ordinary laboratory procedures, including oral passive transfer, were of no value in verifying such a possibility, ingestion experiments were carried out, using varying amounts of methionine and cystine as well as empty capsules and some containing talc as controls. These experiments were done first with the knowledge of the patient but later as a blind study so as to eliminate possible prejudice. In both instances, we were able to show repeatedly that ingestion of methionine was followed by the same symptoms which followed the ingestion of egg, whereas cystine produced only slight symptoms and talc none at all. Demonstration of the existence of allergy to protein split-products (in this case amino acids) would help explain some instances of food allergy with a positive clinical history but negative skin test reactions.

26. ALLERGY AND IMMUNIZATION FOR WASP STING

MARY HEWITT LOVELESS, M.D., NEW YORK, N. Y.

(From the Department of Medicine, The New York Hospital and Cornell University Medical College)

Four adult subjects and two boys have been immunized against wasp stings for one or more seasons during the past six years. Each gave a history of having had, within twenty minutes of receiving one sting, violent urticarial reactions associated with collapse. Immunization was carried on in various ways, ranging from multiple intracutaneous injections during one or more visits to a single depository of the allergen emulsified in mineral oil according to Freund. The allergen employed six years ago was bee venom, since no

yellow jacket allergen was commercially available. Subsequently, extract of the whole wasp, or of its pupae and larvae, was used. This year, venom sacs were surgically removed from anesthetized wasps immediately before dilution for inoculation into the patient.

The degree of allergy existing prior to treatment as well as the resistance acquired during the course were judged by means of controlled tests of the skin and eye. Proof of a high clinical immunity was found during challenge tests with large doses of the immunizing material and, in some instances, with insect stings that were inflicted deliberately in the laboratory or accidentally in the field. Serologic studies failed to reveal either reaginic or precipitating antibodies.

27. HOUSE DUST ALLERGY. I. OCCURRENCE AND INCIDENCE OF SEASONAL PATTERNS OF ASTHMA AND RHINITIS

A. M. Targow, Ph.D., M.D., Los Angeles, Calif.

(From the Division of Allergy, Department of Medicine, University of Southern California School of Medicine)

The present-day conception of the course of symptoms of house dust allergy is that when the symptoms are seasonal they tend to occur primarily during the winter months and to disappear during warm weather. This paper offers evidence to show that the foregoing concept fails to encompass the whole picture. Analysis of the actual course of events in 156 patients sensitive only to house dust shows that any calendar period of the year may serve as a regular annual period of recurrence of seasonal symptoms or of exacerbation of otherwise perennial symptoms. For any one patient, both the duration of the house dust season and the time of the year involved are strikingly constant from year to year. The phenomenon appears to hold true for patients in all parts of the country. Figures are given to show the absolute and relative incidence of the various seasonal patterns that may be encountered. When the season occurs during the summer, the house dust allergy may be confused with pollen allergy. Other implications of the phenomenon for the diagnosis and management of house dust sensitive cases are discussed.

28. FURTHER STUDIES ON BIOLOGICAL PROPERTIES OF STAPHYLOCOCCUS EXTRACT

Murray Dworetzky, M.D., Horace S. Baldwin, M.D., Morton C. Kahn, D.Sc., and Marilyn K. Smart, M.A., New York, N. Y.

(From Cornell University Medical College, Department of Medicine, Allergy Division [M.D. and H.S.B.] and Public Health and Preventive Medicine [M.K.S. and M.C.K.])

Previous studies from this laboratory on the pharmacologic and anaphylactogenic properties of extract made from pathogenic staphylococci washed free of culture medium and exotoxin have demonstrated that this material consistently produces anaphylactoid reactions in intact guinea pigs and contraction of isolated segments of guinea pig ileum.

This work has been confirmed and extended to include comparative studies with culture filtrates of pathogenic staphylococcus and staphylococci toxoid. The effects of these materials upon intact rabbits and guinea pigs and upon isolated suspended segments of guinea pig ileum will be reported.

Studies have also been carried out with rabbit antisera produced respectively by injections of culture filtrates of staphylococcus, toxoid, and extracts of pathogenic staphylococci washed as free as possible of exotoxin, to determine the degree of protection conferred by these three antisera.

29. STUDIES IN BACTERIAL ALLERGY. VI. HAPTENE AEROSOL DESENSITIZATION OF GUINEA PIGS PASSIVELY SENSITIZED TO SPECIFIC PNEUMOCOCCUS POLYSACCHARIDES

OSCAR SWINEFORD, JR., M.D., CHARLOTTESVILLE, VA.

(From University of Virginia)

Our experiments permit the following conclusions to date, Aug. 1, 1953:

1. Type 6 antipneumococcal rabbit serum intraperitoneally sensitize guinea pigs so that an aerosol of type 6 polysaccharide produces reactions varying from moderate dyspnea to anaphylactic death.
2. The results of aerosol and intravenous challenges with polysaccharides are not parallel. Negative aerosol challenges may be followed by anaphylactic death from intravenous challenge.
3. There is a definite threshold of effective concentration of aerosol polysaccharide and of histamine.
4. Desensitization follows exposure to reacting aerosol. The pattern of desensitization varies. It may be noted:
   a. Following recovery, while still in the fog, from moderately severe reactions.
   b. Following several exposures to the fog, each causing decreasingly intense reactions.
   c. Or it may be complete after one severe reaction.
5. Desensitization against one concentration of polysaccharide may desensitize completely to aerosol challenge will respond by anaphylactic death to intravenous challenge of the same strength of polysaccharide. Quantitative factors of time and polysaccharide absorbed have not been studied yet.
6. Local aerosol desensitization does not desensitize against histamine.

30. MORPHINE: A STUDY OF ITS EFFECT ON BRONCHIAL ASTHMA

HOWARD S. MITCHELL, M.D., MONTREAL, QUEBEC, CANADA

(From the Department of Medicine, McGill University)

The harmful effect of morphine in bronchial asthma has been ascribed to the depressing action of the drug on the respiratory center, and possibly to a bronchospastic effect. To study the latter question chain preparations of bronchial muscle of canine and human material were used. No recognizable contraction followed exposure of the preparation to morphine alone. The bronchial chain was washed, and contraction followed exposure to acetylcholine. The bronchial chain was washed again and morphine added to the bath. Addition of acetylcholine now resulted in a contraction greater than that obtained by acetylcholine alone. It appears that morphine renders the bronchial muscle more responsive to acetylcholine.

31. STUDIES ON THE SECONDARY SENSITIZATION OF ANIMALS DURING AEROSOL-INDUCED ANAPHYLACTIC REACTION IN THE ANALYSIS OF THE PATHOGENESIS OF SENSITIZATION

MAX SAMTER, M.D., Z. Z. GODLOWSKI, M.D., AND B. Z. RAPPAPORT, M.D., CHICAGO, ILL.

(From the Department of Medicine and the Allergy Unit of the University of Illinois College of Medicine)

Guinea pigs were sensitized by intraperitoneal injection of egg white. Twenty-one days later they were placed in a respirator sufficiently large to accommodate, simultaneously, ten sensitized animals and ten nonsensitized controls. The air within the respirator was then saturated with nebulized

egg white until the onset of frank clinical symptoms in the sensitized animals.

At the height of the attack of bronchial asthma the asthmatic animals and nonasthmatic controls were exposed to inhalation of ragweed extract containing 0.2 mg. protein nitrogen per cubic centimeter for four consecutive days.

Twenty-one days after the last inhalation of ragweed the egg white sensitive animals and the nonsensitized controls were given 0.5 c.c. of ragweed extract containing 0.2 mg. protein nitrogen per cubic centimeter intracardially. Incidence and severity of anaphylactic symptoms were recorded.

The results are compared with the results of previous studies on the development of sensitivity to ragweed by inhalation in animals pretreated by the inhalation of Piromen. The clinical significance of the findings is discussed.

32. CULTURES OF IMMUNOLOGIC STUDIES OF TISSUE IN HODGKIN'S DISEASE

JACK M. ROSE, M.D., AND JACK R. PULLIAM, B.S., HOUSTON, TEXAS

(From the Department of Medicine, Baylor University College of Medicine)

These studies were undertaken to determine whether Hodgkin's disease tissue had any specific immunologic properties which were distinct from those possessed by normal lymph node tissue. Rabbits were injected with a homogenate prepared from Hodgkin's tissue along with adjuvants. Sera from these animals were freed of all nonspecific antibodies by absorption. Use of the absorbed antiserum created visible damage to the living growing Hodgkin's cell in tissue culture while control rabbit sera were without such effect. The effects of such antiserum on Hodgkin's cells were observed by time-lapse cinematography of a special perfusion chamber under the phase contract microscope. Because of the development of an antiserum of a higher specificity, after preliminary tissue culture studies had already been performed, these studies will be repeated to observe for more definite evidence of cell damage or death.

The antiserum employed in the tissue culture experiments has been tagged with radioactive iodine in order to trace its localization in the bodies of individuals with Hodgkin's disease. Radioautographs of Hodgkin's tissue treated in vitro with the tagged antiserum are being checked against the corresponding histologic section to determine areas of localization in the individual cell as well as the type of cell in which uptake occurs.

33. ALLERGIC DERMATITIS TO ASPARAGUS; A CASE PRESENTATION

WALTER R. KESSLER, M.D., AND JAMES H. BARNARD, M.D., NEW YORK, N. Y.

(From The Institute of Allergy, Roosevelt Hospital)

A case of dermatitis due to hypersensitivity to asparagus in a 54-year-old woman will be described. The lesions appeared mainly on the right cheek and developed within several hours after the ingestion of asparagus. The massive vesicular lesion will be described in detail and kodachrome slides will be shown demonstrating various aspects of the case.

A similar lesion was produced by rubbing raw asparagus on the lesion site when it was in a normal state.

Patch tests with cooked and uncooked asparagus applied to other areas were negative.

The characteristics of fixed drug eruptions, the present lesion, and other cases of dermatitis due to food sensitivity will be made.

The results of passive transfer studies with fractionated portions of asparagus will be described.

This case suggests that the mechanism involved in cases of intrinsic and extrinsic (contact type) dermatitis is identical.

34. TOPICAL USE OF HYDROCORTISONE (COMPOUND F) OINTMENT IN ALLERGIC DERMATOSES

SIDNEY FRIEDLAENDER, M.D., AND ALEX S. FRIEDLAENDER, M.D., DETROIT, MICH.

This study covers one year's experience in the topical use of hydrocortisone in approximately 100 patients (infants, children, and adults) with allergic eruptions, the majority of whom fall into the classification of atopic dermatitis. In contrast to previous negative experience with topically applied cortisone in such cases, local Compound F in concentrations of 1 to 2.5 per cent produces an immediate favorable response in the great majority of those treated. Such improvement may be sustained by daily use over a period of many months, although tolerance develops in some instances after long-continued application. The best response occurs in oozing vesicular, scaly, lichenified, and excoriated lesions, especially where the skin is broken, and is least effective in urticarial, papular, and deep vesicular eruptions where the skin is intact.

Comparisons of hydrocortisone (alcohol) and hydrocortisone acetate indicate that there is no essential difference in their local action. A 2.5 per cent concentration was found more uniformly effective for initial use than a 1 per cent preparation, although subsequent maintenance with the lesser strength was frequently possible. Combinations of hydrocortisone and 0.5 per cent neomycin were found particularly effective in the rapid control of secondarily impetiginized eruptions.

35. URTICARIA AND ANGIONEUROTIC EDEMA: STATISTICAL SURVEY OF FIVE HUNDRED CASES

MILTON J. STEINHARDT, M.D., ANN ARBOR, MICH.

(From the Department of Medicine, University of Michigan Medical School)

An analysis of 500 consecutive unselected cases of urticaria and angioneurotic edema seen at the University Hospital, Ann Arbor, Mich., will be presented. For arbitrary reasons and because of change in trends in therapy, the patients are divided into those seen during 1942 to 1947 inclusive and those examined during 1948 to 1953.

The incidence of urticaria was found to be greatest in the third and fourth decades of life. An allergic family history of asthma, hay fever, and/or urticaria was recorded in 31 per cent of the cases reviewed, while a positive personal allergic history was found in 43 per cent of the total patients studied.

Positive skin reactions were found in 60 per cent of those patients tested and in 30 per cent of total cases observed.

An analysis referable to etiology suggested the importance of emotional factors as recorded on case histories compiled from many different examiners.

The period in which penicillin had been used in a great number of patients was marked by a twofold increase in urticaria related to drug etiology.

Physical agents as a cause of urticaria showed an increase in incidence from 1 per cent to 7 per cent.

The relative numerical importance of food and drug allergens, and the role of infection in urticaria and angioneurotic edema will be discussed.

Angioneurotic edema in association with urticaria showed a considerable increase in the 1948 to 1953 period as compared to the 1942 to 1947 period. A possible explanation for this increase will be discussed and the results of treatment with different medications will be evaluated.

Abstracts of Papers to Be Read by Title

36. ALLERGIC REACTIONS AND CARDIAC SYMPTOMATOLOGY

CLARENCE BERNSTEIN, M.D., AND S. D. KLOTZ, M.D., ORLANDO, FLA.

The symptomatology of allergic reactions depends upon the site or organs involved in the tissue reaction. In the past, the clinical practice of allergy has focused attention largely on the respiratory tract and on the skin. A group of cases of allergic origin, presenting cardiac symptomatology, such as so-called rheumatic heart disease, angina pectoris, coronary episodes, and paroxsymal tachycardia, was reported in 1949. The possible mechanisms involved were elucidated. Since that time further observations on an increasing amount of clinical material have extended the study and borne out the original conclusions. Fifty-four patients presenting complaints, possibly referable to the heart, and in many instances so diagnosed, were subjected to allergic study. Many of these individuals under allergic management were shown to gain dramatic and often lasting relief from their disabilities. The allergy burden has at times been only a contributory factor to the patient's overload, and therapy along these lines has frequently hastened recovery. Consideration is given to the probability that many of these individuals had vessels already narrowed with atheromata so that a minimal constriction produced circulatory symptoms. While allergic factors are present in but a small segment of all cases in this general heart disease category, any appreciable additional improvement in the clinical condition and course is desirable. If this type management can reclaim any actual or potential cardiac cripple, the possible help to be gained from the allergic approach is warranted.

37. CLINICAL SENSITIVITY TO PETROLEUM, COAL, GAS, PINE, AND THEIR DERIVATIVES

THERON G. RANDOLPH, M.D., CHICAGO, ILL.

The ubiquitous exposure to petroleum, coal, gas, pine, and their various combustion products and derivatives has retarded the recognition of their apparent allergenic properties. There has been little comprehensive effort to associate the responses resulting from contactant, inhalant, ingestant, and injectant exposures to the antecedents and derivatives of petroleum as composite parts of a clinical picture associated with allergic disease. These materials have usually been regarded as irritants. The fact that ordinary exposure to these petroleum products is effective in inducing allergic type symptoms in certain individuals having the tendency for allergic disease and that this often occurs after an infinitely small contact suggests the presence of allergenic as well as irritant properties. The term "petroleum sensitivity" has been applied in this clinical sense although an immunologic basis for sensitization has not been demonstrated.

The major sources of petroleum, coal, gas, and pine judged to be significant in 100 advanced instances of clinical petroleum sensitivity are described. Aspirin sensitivity and sulfonamide sensitivity existed in approximately 50

per cent. Clinical responses encompass the range of known allergic reactions. Clinical petroleum sensitivity is best detected by means of a detailed history. Advanced instances are usually associated with multiple sensitization, including specific allergy to foods, drugs, and particulate inhalants. When house dust allergy coexists, therapy with phenol-free house dust extract is particularly helpful but the avoidance of exposure to petroleum, coal, gas and pine, as far as this is possible, represents the major approach in therapy.

38. AEROBIC BACTERIA IN HOUSE DUST

MORTON C. KAHN, D.SC., K. MARILYN SMART, M.A., HORACE S. BALDWIN, M.D., AND MURRAY DWORETZKY, M.D., NEW YORK, N. Y.

(From the Department of Public Health and Preventive Medicine and the Department of Medicine, Allergy Division, Cornell University Medical College, New York Hospital)

Bacteriologic investigations were carried out on weighed portions from thirty-eight varied samples of house dust. These were cultured aerobically. Colonies were then isolated and differentiated morphologically and biochemically. Strains isolated were chiefly saprophytic forms of the following families: Bacillaceae (present in 100 per cent of dust samples), Micrococcaceae (89 per cent), Bacteriaceae (58 per cent), Corynebacteriaceae (45 per cent), Enterobacteriaceae (26 per cent), Neisseriaceae (11 per cent), and Lactobacteriaceae (3 per cent).

In order to check the admittedly empirical culture method, eight of the dust samples were cultured a second time, and these duplicate samples paralleled the original results. Gross bacterial counts from 48 hour agar pour plates of ten varied dust samples showed a wide range—from 29,000 colonies per gram to 4,038,000 colonies per gram. The average count for the ten samples was 1,802,850 colonies per gram.

This study indicates that the bacterial flora in house dust varies widely both qualitatively and quantitatively.

39. A STUDY OF AN ALLERGENIC FLAVONOID GLYCOSIDE DERIVED FROM EXTRACTS OF TIMOTHY POLLEN

MARY C. JOHNSON, A.B., STANLEY F. HAMPTON, M.D., ALINE W. SCHIELE, A.B., AND SAM FRANKEL, M.A., ST. LOUIS, MO.

(From the Department of Medicine, Washington University School of Medicine)

Crystals often appear spontaneously in both plain and glycerinated extracts of certain grass pollens. Since we encountered skin reactivity to the isolated crystals, a study was undertaken to identify them chemically and to evaluate their allergenic activity. The greatest yields of the crystals (0.3 per cent) were obtained from the ethanolic Soxhlet extractions of ether defatted pollen. In 1931, Moore and Moore designated as "dactylin" similar crystals which they isolated from extracts of timothy and orchard grass pollen. They established the formula of these crystals provisionally as $C_{23}H_{28}O_{15}$, and suggested that they were a glucoside closely related to the hydroxyflavones. Stull and associates (1932) also reported their presence in extracts of timothy pollen.

In the present investigation, we made use of chromatographic methods for the study of flavonoids as recently described by Bate-Smith and Westall; and Gage, Douglass, Casteel, and Wender. In all chromatographic studies multiple solvents were employed. The aglycone obtained on hydrolysis of the glycoside yielded Rf's, color and UV characteristics identical with simultaneously processed quercetin. The intact glycoside behaved differently from simultaneously processed isoquercitrin, quercitrin, and quercetin. The soluble

hydrolysis end product of the glycoside was identified chromatographically as glucose. Spectrographically the aglycone and quercetin, individually and mixed, have identical patterns in three solvents. Spectrographs of the glycoside in neutral solvents have a characteristic trough at 260 γ and, in this respect, differ from those of isoquercitrin, quercitrin, and quercetin.

Intradermal tests with the glycoside on 24 timothy-sensitive cases resulted in ten negative, eleven slight, and three marked reactions. Particular interest attaches to this crystalline compound since it is a non-nitrogenous, low molecular allergenic fraction of pollen in relatively pure form. Additional studies of chemical and allergenic properties are in progress.

40. CATHODE RAY THERAPY FOR DISSEMINATED NEURODERMATITIS

JOHN L. FROMER, M.D., BOSTON, MASS.

(From the Department of Allergy and Dermatology, The Lahey Clinic)

Most cases of generalized disseminated neurodermatitis and/or exfoliative dermatitis of the chronic type may be managed in a very satisfactory way by routine allergic and dermatologic therapy. Patients who have been treated in this way and who are still refractory to topical, immunologic, and x-radiation may now be given generalized doses of beta electrons or cathode rays. This is accomplished by exposing the entire body at one sitting to these rays.

This paper reports 4 patients in the last year who have been treated with this new modality which emits beta electrons of controlled penetrability so that none of the ionization energy reaches beyond 1 cm. below the skin surface. Thus far there have been no untoward effects from this type of irradiation. A brief description of the physics of the radiation will be discussed. Kodachrome slides of these patients before and after treatment will be presented.

There are no previous reports in the literature on the treatment of disseminated atopic dermatitis or exfoliative dermatitis with this method since the apparatus has only recently become available at the Massachusetts Institute of Technology, Cambridge, Mass. The author has reported the use of beta or cathode rays in lymphomas of the skin and this is a new approach to the treatment of chronic neurodermatitis and exfoliative dermatitis of a generalized nature.

This is a preliminary report. All 4 patients are now in satisfactory remissions. The practical aspects of this type of therapy will be presented.

41. SOME PROBLEMS IN MAINTENANCE CORTISONE THERAPY

WALTER R. MCLAREN, M.D., AND D. EDWARD FRANK, M.D., PASADENA, CALIF.

Twenty-four cases of intractable allergic disease were treated with large doses of cortisone and adjuvants for six to ten months. Seven patients were children. Twenty-three had asthma, 13 emphysema (4 had cor pulmonale), 2 severe neurodermatitis, and 1 multiple sclerosis as well as asthma.

Cortisone doses usually started at 200 mg. per day for adults and 100 mg. for children, decreasing as indicated to 75 or 37.5 mg., respectively. Adjuvants used were low sodium diets, high potassium intake (up to 12 grams KCl a day), Dinestrol, 0.1 to 0.5 mg. per day, methyltestosterone, 75 to 100 mg. per week, anticholinergics in full doses, and ascorbic acid, 100 to 500 mg. per day.

Despite the high cortisone doses used only 10 of 24 patients (42 per cent) had substantial relief of symptoms, and only 1 (10-year-old boy with asthma)

was completely clear on a dosage level that could be tolerated. Five patients had fair relief of symptoms, but only at the cost of a mild Cushing's syndrome. Nine patients were made worse or had severe complications and discontinued treatment within a month. It appeared impossible to clear up symptoms completely in the majority of these patients with any practical dosage level.

Among the expected complications that did not develop were excessive increase in blood pressure (average systolic rise 20 mm. and no diastolic over 100 mm.), diabetes, bone demineralization, cutaneous striae, psychoses, thyroid depression, or detectable gastrointestinal ulceration.

Weight gain was a problem in 7 patients. It was not controlled by large amounts of potassium and low salt diet, often came only after the cortisone dose had been reduced, and seemed caused by edema at first but later by overeating. Appetite increased so much that these patients could not stay on a diet, and anticholivergics or dextroamphetamine had little effect. Fourteen patients gained less than 10 per cent, and three actually lost weight on cortisone. Edema was a problem in 7 patients, coming early in treatment with high doses of cortisone, and was relatively unaffected by electrolyte control or diuretics. Only lowering cortisone dose had any effect. Intercurrent infection was a problem in 5 of the 7 children and in 3 of the adults. Recurrent infectious asthma and boils responded rapidly to antibiotics but not to increased cortisone dosage. Five cases of acne responded poorly to the usual skin care. One girl developed a heavy growth of face and body hair in spite of adequate estrogen dosage. One 8-year-old boy showed some growth of primary and secondary sex characteristics.

Nine patients (27 per cent) had to discontinue cortisone. Five of these were older patients with emphysema and probable pulmonary hypertension. All became much more dyspneic, either immediately before weight gain appeared or within a few weeks. Other reasons for stopping treatment were severe cardiospasm, headache, nervousness, and fear of cortisone. Two patients had x-ray evidence of healed apical tuberculosis which did not change in over eight months of treatment. One patient on low cortisone dosage, with an old quiescent tuberculous hip, developed a new abscess which had to be drained after two months.

It appears that cortisone with adjuvant therapy does not cure or control completely symptoms in chronic intractable allergic disease, nor are some of the complications of treatment easily controlled.

42. HISTOPATHOLOGY OF THE ALLERGIC REACTION OF THE NOSE

RAYMOND S. ROSEDALE, M.D., CANTON, OHIO

(From Mercy Hospital)

Photomicrographs in color illustrate the various tissue changes in allergic mechanism of the nose. Original study is from biopsies. Included are the normal mucosa, the various changes in the vessels, the stroma, the glands and cilia, the genesis of polyps, complications, degenerative and permanent changes impairing nasal physiology. (Illustrated.)

43. THE EFFECT ON NORMAL RECIPIENT ANIMALS OF INTRAPERITONEAL IMPLANTATION OF TISSUES FROM SENSITIZED AND SHOCKED GUINEA PIGS

WILLIAM PIEPER, M.S., AND MAX SAMTER, M.D., CHICAGO, ILL.

(From the Allergy Unit, University of Illinois College of Medicine)

In previous experiments we have shown that the implantation into the peritoneal cavity of normal guinea pigs of lungs from guinea pigs which died in anaphylactic shock produces a marked increase in the circulating eosino-

phils of the recipient twenty-four hours after transfer. During the course of the study we noticed that the recipients developed an extraordinary sensitivity to the antigen which had been used to sensitize the donors. Moreover, it was found that the sensitivity produced by the transfer of lung tissue exceeded the sensitivity produced by the transfer of other tissues of equivalent antibody content.

The present study attempts a further analysis of this incidental observation. Guinea pigs were sensitized by intraperitoneal injection of egg white. Three weeks later one-half of the sensitized animals were sacrificed by intraperitoneal injection of Nembutal; the other half by intracardial injection of the specific antigen. Equivalent weights of skin, intestine, uterus, and lungs were then transferred into the peritoneal cavity of normal recipients. Twenty-one days after transfer, one-half of each of the groups receiving sensitized tissues and one-half receiving the tissues of animals which had been shocked were sacrificed by intracardial injection of egg white. The other half of the animals was protected by intraperitoneal injection of Benadryl thirty minutes prior to the intracardial injection of egg white, and allowed to live for twenty-four hours. At that time the animals were sacrificed by intraperitoneal injection of Nembutal. Skin, lung, intestine, and uterus were removed for histologic examination.

The paper reports:

1. The incidence of fatal anaphylactic shock in normal recipients three weeks after implantation of various tissues from sensitized and shocked donors.

2. The distribution of eosinophils in lungs, skin, intestine, and uterus of recipients twenty-four hours after the intracardial injection of egg white.

44. PREVENTION OF REACTIONS IN INTRAVENOUS UROGRAPHY

S. William Simon, M.D., Henry I. Berman, M.D., Hans F. Plaut, M.D., and Saul A. Rosenblum, M.D., Dayton, Ohio

(From the Allergy Clinic, Brown General Hospital)

It has been customary in the past few years to give some antihistamine orally previous to the intravenous injection of the contrast medium. In spite of such precautions, in a series reported, about 5 per cent of the patients experienced general reactions and of these approximately 20 per cent were described as "severe."

This study was undertaken in order to simplify and standardize the procedure and, if possible, to reduce the rate and severity of reactions. Due to conflicting results, sensitivity tests have been discarded. Histories, particularly of past or present allergy, were taken but our procedure was the same with every patient.

In each case 2.5 ml. of Chlor-Trimeton Maleate solution, containing 5 mg. of the drug, was mixed in the syringe with the contrast medium (Diodrast, Neo-Iopax, or Urokon Sodium) to be injected. One milliliter of this mixture was given intravenously as a test dose and with the needle in the vein a pause of approximately one minute was allowed to determine individual tolerance. If no adverse reaction occurred, the remainder of the solution was injected quite rapidly. Dye-antihistamine mixtures were given to 332 patients as follows: Diodrast 159, Irokon 53, and Neo-Iopax 120. There was a history of allergy in 26 or 8 per cent.

The reactions noted were chills in three (two of which were delayed), warmth or flush in 12, arm pain in eight, nausea in 12, vomiting in two, mild urticaria in one, severe urticaria in one, dizziness in two, sneezing in two, wheezing in two, and burning of lips, throat, or rectum in four. Only the

urticaria, sneezing, and wheezing can be considered allergic reactions and these occurred in six patients (1.8 per cent). Except for the one severe urticaria, all other reactions were mild and disappeared quickly, usually without any further treatment.

An analysis of the various reactions with each drug and case reports is given.

45. THE BLOOD CHEMISTRY AND ASSAY STUDIES OF 112 CASES OF ALLERGIC INDIVIDUALS

NATHAN E. SILBERT, M.D., CHELSEA, MASS.

(From the Department of Allergy, Lawrence Quigley Memorial Hospital)

Previous studies and reviews of the literature of the vitamin C content of the blood reported by this author prompted more intensive blood studies in an effort to determine the existence, if any, of a fixed pattern of vitamin and/or mineral deficiencies.

The diagnosis of true allergy was confirmed by history, physical examination, and diagnostic allergic studies together with routine blood counts and x-rays of the paranasal sinuses and chest. The chemical analysis and blood chemistries were then done. These findings are reported. It can be established that fixed patterns develop. This study shows definite trends to indicate a decrease in the vitamin A, vitamin B_2, vitamin C, and vitamin E contents of the blood, together with definite decreases in the unsaturated fatty acid content.

It has also been established that when massive therapeutic doses of vitamins and unsaturated fatty acids are administered during the early periods of desensitization to the offending allergens, a definite decrease in all of the vitamin deficiencies manifests itself within a period of three months. When the desensitization process has increased the immunity to the offending allergen(s), the removal of medication can be instituted. The purpose of the paper is to establish clearly that the allergic individual follows the pattern of vitamin deficiencies.

46. THE EPIGASTRIC SYNDROME OF ALLERGY

ALBERT H. ROWE, M.D., ALBERT ROWE, JR., M.D., AND KAHN UYEYAMA, M.D., SAN FRANCISCO, CALIF.

The symptoms which we call the epigastric syndrome of allergy are, with varying frequency: epigastric pressure, fullness, burning, soreness, aching, pain, and distress, and, with less frequency, nausea, sour stomach, belching, and vomiting. Burning, pressure, and/or aching also may occur under the sternum, radiating laterally into the chest. When under the lower sternum, the xiphoid is often tender and a pseudo-angina may occur; when under the upper sternum, the distress often radiates into the chest and soreness and aching in either side of the neck and even in the throat may result. Soreness, cramping, and pain in the rest of the abdomen may also occur and the bowels may be loose or constipated, with or without mucus. In many patients nervousness, restless sleep, and depression ensue. Allergic fatigue and toxemia and allergic headaches in varying degrees may exist. Other manifestations of allergy may also occur in the patient, although the gastric and other tissues in the epigastric area may be the only shock organs of allergy. In many of these patients negative roentgen-ray studies of the gastrointestinal tract and gall bladder, negative laboratory studies, including stool and gastric analyses, and failure of relief from medical treatment have led to the diagnosis of psychoneurosis.

The frequency of these various symptoms in over 50 relieved patients studied in our private practice and in the Gastrointestinal Clinic of the Uni-

versity of California in the last five years will be shown in charts. The results of x-rays and laboratory studies will also be tabulated. The control of the symptoms with the effective elimination diet in the presence of demonstrated duodenal ulcer in a few of these patients with the epigastric syndrome of allergy has encouraged another study of allergy as a possible major cause of duodenal ulcer.

The fruit-free elimination diet with rice and often with milk, with which the control of these symptoms usually occurs, and the subsequent manipulation of the diet to determine gradually the allergenic foods responsible for this epigastric syndrome of allergy will be discussed. The infrequent necessity of using any drugs for relief, in addition to the elimination diet, emphasizes food allergy as the sole or major cause.

47. CONTRIBUTION TO THE STUDY OF THE RETICULOENDOTHELIAL ORIGIN OF ALVEOLAR MACROPHAGES. VII. THEIR BEHAVIOR WHEN CONFRONTED WITH MARKED ANTIGENS IN GUINEA PIGS WITH EXPERIMENTAL ASTHMA

E. A. Pedace, M.D., and A. E. Bachmann, M.D., Buenos Aires, Argentina

Intraperitoneal administrations of Evans' blue, horse serum mixed with Evans' blue, and horse serum diazotized with Evans' blue were compared in guinea pigs sacrificed at various intervals, in order to follow the evolution of these substances within the organism. Some of the animals were submitted to the so-called experimental asthma brought about with nebulization of horse serum only. The behavior of the alveolar macrophages was followed. It was observed that the animals injected with Evans' blue as well as those receiving horse serum mixed with Evans' blue showed a dye distribution completely different from those injected with Evans' blue diazotized with horse serum. In the latter, the dye was found within the macrophages, within the vascular adventitiae, exudates, and interalveolar septa. These facts confirm our previous work in favor of a reticuloendothelial origin of the alveolar macrophages.

48. LONG-TERM THERAPY USING ANTIBIOTICS AND CHEMOTHERAPY IN ASTHMA ASSOCIATED WITH INFECTION

Charles B. Shuey, M.D., and William C. Grater, Dallas, Texas

(From Southwest Medical School, University of Texas)

An increasing number of patients with wheezing or symptomatic asthma without demonstrable allergic etiology have come to our attention. Many of these patients undoubtedly have chronic low-grade respiratory infections. It has occurred to us that since adequate treatment of known chronic infections such as tuberculosis and actinomycosis has necessitated long-range antibiotic therapy, the same might be true in asthma associated with infection.

It is often difficult to establish the important current etiologic factors in an individual asthmatic episode. In such a case are we dealing with a superimposed infection or a demonstrable clinical allergy? Cultures of these secretions will show bacteria varying as to species, season, and virulence. For this reason cultures have not given consistent results. The value of skin tests with fractions of bacterial products (nucleoprotein, carbohydrate, etc.) is questionable. The literature abounds with the importance of infection in acute asthmatic episodes in children. There is a variation in the opinion of many regarding the effect of an intercurrent respiratory infection on the allergic patient. Antibiotics have been successfully used in asthma associated with acute respiratory infections. Fishman reported the successful use of a sulfonamide mixture in the prophylaxis of recurrent infective asthma in twenty patients who failed to respond to allergic or other treatments.

In a study of twenty-five patients we believe we can state that the great majority received considerable benefit from both a therapeutic and a prophylactic standpoint. The data collected on each patient consisted of an allergic survey including history, physical examination, skin tests, chest and sinus x-rays, nasal smears for eosinophiles, and Gram stain of sputa. The pulmonary function was evaluated both before and during therapy by subjective information from the patient, followed by chest examination and finally by determining the vital capacity and maximal breathing capacity.

Treatment consisted of various combinations of the following for periods ranging from one to six months: (1) Aqueous procaine penicillin in 300,000 unit doses three times weekly; (2) streptomycin, 0.5 Gm., and dihydrostreptomycin, 0.5 Gm., three times weekly; (3) Gantrisin was used in doses of 1 Gm. four times daily.

From our results it would seem to indicate that such long-term antibiotic or chemotherapy may be important in the treatment and prevention of asthma.

49. HYPOALLERGENICITY OF SULFAMETHATHIADIAZOLE

S. H. Jaros, M.D., Valhalla, N. Y.

(From the Allergy Clinic, Grasslands Hospital)

There has been in the recent past, a recrudescence of interest in the sulfonamides in view of the apparent increase in occurrence of fatal hypersensitivity reactions to antibiotics. In the past few years several new sulfonamides have been developed, one of which has been received with acclaim and usage in Europe, namely, sulfamethylthiadiazole. This new sulfonamide has created a good deal of interest in this country. Preliminary clinical reports show this compound to be of high clinical efficacy. It is characterized by a high degree of solubility, a wide range of pH, and rapid absorption and excretion. There is no occasion for the concurrent administration of alkalies, nor the need for forcing fluids. Actually, fluids can be restricted if so desired. The compound has an extremely low toxicity and is virtually free from hazards of hematuria and crystalluria. In view of the past literature concerning the ability of sulfonamides to cause sensitivity reactions, this agent was subjected to clinical studies wherein dosages of 4 Gm., orally, daily were offered to patients with known hypersensitivity reactions to other sulfonamides, as well as to another huge group of patients who were known to be allergic individuals. Patch tests using several sulfonamides are compared and illustrated. Up to the present time, no hypersensitivity reactions have been seen with the administration continued up to twenty-two days.

50. PATHOGENESIS OF IRREVERSIBLE VASCULAR LESIONS IN THE ALLERGIC ANIMAL

Clement L. Sullivan, M.D., St. Louis, Mo.

(From the St. Louis University School of Medicine)

It is admitted that union of circulating antibody with a specific antigen causes immediate dynamic vascular changes and that the union of cellular antibody with the antigen is followed by delayed connective tissue lesions (fibril edema, infiltration of cells). Nevertheless, the simple union of antibody and antigen is not a satisfactory explanation for the pathogenesis of the irreversible vascular lesions (thrombosis, hemorrhage, necrosis) which occur in the presence of antibody and antigen. Failure of the involved tissues to excrete, or to metabolize the mass which results from antigen-antibody union is a more likely explanation for the pathogenesis of these and related lesions, which also can be produced in complete absence of antibody. The experimental allergy literature has been reviewed, divided into groups, and summarized in order to demonstrate this principle.

Announcement

The American Academy of Psychosomatic Medicine

On May 31, 1953, at the Plaza Hotel in New York City, a new Society named The American Academy of Psychosomatic Medicine was founded. The specific object of its incorporation is to be the advancement of the scientific knowledge and practice of those aspects of medicine which relate to the interaction of mind, body, and environment by means of study, laboratory and clinical research, meetings, and discussions in cooperation with other workers in these and related fields.

Membership will consist of Charter Fellows, namely, those who enrolled at the previous meeting held one year ago, and Founding Fellows (those who join before the first of January, 1954). The Constitution allows for Honorary and Emeritus Fellows.

The requirements for membership as Fellow can be obtained from the Secretary, Ethan Allan Brown, M.D., 75 Bay State Road, Boston, Mass.

The other officers elected at the Founding meeting included Dr. William Kaufman, of Bridgeport, Conn., President, Dr. B. B. Raginsky, of Montreal, Canada, Vice-President, and Dr. Alfred J. Cantor, of Flushing, N. Y., Treasurer.

The first scientific meeting will be held in New York City in June, 1954.

Details concerning the new Society may be obtained from the Secretary, or the other officers.

Course at University of Pittsburgh

The American College of Physicians will conduct a course at the University of Pittsburgh, School of Medicine in "Diseases Due to Allergy and Immune Mechanisms," for the week beginning with Monday, May 17, 1954. This advanced course will be for physicians already engaged in the practice of allergy. It will consist of didactic presentations, laboratory demonstrations, and panel discussions in which the registrants will participate. All those interested please address your inquiry at your earliest opportunity to Leo H. Criep, M.D., The Bigelow, Bigelow at Tunnel Streets, Pittsburgh 19, Pa.

Openings in One-Year Residency in Allergy

The Medical Center, School of Medicine, University of Pittsburgh, and the United States Veterans Hospital, Pittsburgh, Pa., announce several openings in a one-year residency in allergy. This includes clinical and laboratory training as well as teaching experience. The salary is $1,500 to $3,300 per annum. Address inquiries to Leo H. Criep, M.D., The Bigelow, Pittsburgh 19, Pa.

Brazilian Society of Allergy

Dr. E. Brum Negreiros, of Rio de Janeiro, has recently been elected President of the Brazilian Society of Allergy. This Society has also designated Dr. Negreiros to take charge of the plans for the Second International Congress on Allergy to be held in Rio de Janeiro in the fall of 1955 under the auspices of the International Association of Allergology. The exact dates of this meeting have not as yet been formally announced.

Correspondence

Copenhagen, October 29, 1953

To the Editor:

In the July, 1953, issue of this JOURNAL, page 371, Drs. Ratner and Silberman published an interesting paper entitled: "Critical analysis of the hereditary concept of allergy." One of their conclusions is that "An evaluation of the available data does not satisfactorily demonstrate that, within the scope of the antigen-antibody mechanism, the capacity to become sensitized is controlled by genetic influences." In their paper the authors report their own percentages of allergic diseases in various groups of persons, and these results deserve a few comments:

In a group of 3000 individuals (medical students, physicians and nurses) the incidence of allergic diseases was found to be 10-18 per cent, whereas in a group of 250 allergic patients plus their relatives, a total of 6,244 individuals, the incidence of allergic diseases (including the 250 patients) was calculated to be 9.8 per cent (617 out of 6,244). According to Ratner and Silberman these values show that allergic diseases are not more common in allergic families than in a normal series.

Their series, however—provided that they are comparable—permit even more far-reaching conclusions, viz., that allergic diseases are less common in the relatives of allergic patients than in the normal population!

In the normal series of 3,000 persons Ratner and Silberman found the incidence of allergic diseases to be a minimum of 10 per cent. In the allergic population the incidence of allergy was found to be 9.8 per cent. The actual incidence of allergic diseases *in the families* of the 250 allergic patients—the value with which the normal incidence must be compared—is (617 - 250 =) 367 out of (6,244 - 250 =) 5,994, in other words 6.1 per cent, i.e. considerably lower than the 10 per cent in the normal series.

A statistical calculation of these incidences with the χ^2 test gives:

$$\chi^2 = 51.8;\ f = 1;\ P << 0.001.$$

That is to say, Ratner and Silberman's figures show an extremely significant probability that allergic diseases are more common in a normal series than in the relatives of allergic subjects.

No other workers have made similar findings, and it must be permissible—pending further publications—to doubt the correctness of these authors' results.

The explanation of this peculiar result is probably a widely different nature of the two series. Ratner and Silberman do not mention which diseases have been reckoned as allergic in the two groups. Also, they do not state which categories of relatives the 5,994 persons comprise or whether all these 5,994 persons were examined for allergic diseases in the same way as the 3,000 physicians, medical students and nurses of the normal series. It would be interesting to learn.

MICHAEL SCHWARTZ, M.D.

Received for publication Nov. 16, 1953.

Sept. 29, 1953

To the Editor:

In the panel discussion on penicillin sensitivity in the last issue of the JOURNAL, Dr. Sheppard Siegal mentions that some cases of urticaria, following penicillin sensitivity, may last from six to fifteen months. I have often wondered whether our patients are getting penicillin in their daily diet. A source of penicillin which may be overlooked is penicillin which may be present in the daily milk supply.

In discussing this with Dr. Oscar Sussman, Chief of the Bureau of Veterinary Public Health of the State of New Jersey, I was referred to the following three articles:

1. Krienke, W. A.: Penicillin in Milk, Milk Plant Monthly, December 1949.

2. Hunter, G. J. E.: The Effect of Penicillin in Lactic Streptococci, The Effect of Penicillin in Milk on the Manufacture of Cheddar Cheese. Journal of Dairy Research, Vol. 16, 39-45, January 1949.

3. Hunter, G. J. E.: A Note on the Effect of Penicillin on the Reductase Test for Milk Quality. Journal of Dairy Research, Vol. 16, 149-151, October, 1949.

There does seem to be a definite indication that there is a residual amount of penicillin remaining in milk after penicillin udder therapy either by veterinarians or farmers themselves. This may be a cause for some of the reactions in our patients who at some time or other show symptoms of clinical allergy to milk and at other times seem to handle milk with no difficulty.

Daily milk delivery in large cities usually consists of pooled milk, some of which at some time contains great quantities of penicillin and at other times contains none. Pasteurization does not seem to destroy the antigenicity of penicillin.

Sincerely yours,

FRANK L. ROSEN, M.D.

Book Reviews

Series of 4 pamphlets: Allergy Is Everybody's Business; Breathe Easy; One Man's Food; Skin Deep. Samuel M. Feinberg, M.D. Published by Blue Print for Health, Room 1206, 425 North Michigan, Chicago, Ill. Price, 10c each.

Dr. Samuel M. Feinberg should be congratulated upon his ability to explain simply, in lay language, the intricacies, complexities, and complications which beset the individual with an allergic constitution. It is trite to say that such a task is more difficult in many respects than the writing of an article in medical or scientific parlance for the physician. Dr. Feinberg has done well his task of explaining to the public the several important allergy forms in the folders. The first of these folders entitled "Allergy Is Everybody's Business" is concerned with general allergic problems. The second entitled "Breathe Easy" is concerned with the respiratory allergies, while the third, "One Man's Food," discusses food allergy. The fourth, "Skin Deep," describes the cutaneous allergies. These publications were prepared by the Blue Cross Commission as its contribution toward the better understanding by the public of the several forms of allergy. In simple language, the nature of the conditions, usually ambulatory, is described, their characteristics, symptoms, implication, as well as the modes of treatment, being discussed. Most physicians would profit by the reading of them.

It would be readily implied that by proffering such publications, the Blue Cross Commission not only recognizes the importance of educating the public in allergic matters but also is prepared to reimburse the patient member for his expenses incurred in the diagnosis and treatment of his ambulatory allergy. Both patient and physician, however, have learned to their disappointment and disillusionment that such is not the case and that payments offered are niggard, ridiculously small, in amount. This policy has led to the loss of good will and has provoked a marked feeling of irritation and resentment directed not only toward the Blue Cross and Blue Shield but also toward the innocent physician who shares in the criticism because he failed to warn the patient in advance of what to expect.

It is doubtful, therefore, that there will be any wholehearted cooperation of the physician in the placing of these folders upon his waiting room table, since by so doing he would appear to endorse not only the contents, which he could readily do, but also the attitude of the Blue Cross Commission toward expenses incurred for allergic ailments, a situation which he probably deplores. The problem of inducing the physician to exhibit the folders might be solved partially by the inclusion in each folder of a statement prominently placed that the publications were for educational purposes and did not constitute an invitation to the patient to apply for reimbursement for any expenses incurred in the treatment of his allergic complaint, unless he be hospitalized.

W. C. S.

The Allergic Patient and His World. Florence Eastty Sammis, M.D. Springfield, Ill., Charles C Thomas. Price, $4.75.

With the emergence of the physician from the days when he practiced his profession in a frock coat, wrote his prescriptions in Latin and carefully shielded the lay individual from any knowledge of medical matters has come the revelation that the enlightened patient is usually the one who can be the most cooperative and the most successfully treated. This fact is particularly true in the handling of problems of clinical allergy, where it is being increasingly realized by the physician that his responsibility is one of education of the patient as well as one of actual medical therapy. It is essential for the

attainment of successful results in treatment that the individual suffering from hay fever, bronchial asthma, and other allergic maladies understand the nature of his disease. This requires time and patience of both physician and patient, as Dr. Sammis has realized. She has made a successful attempt to provide the patient with a handbook, explaining in simple language and lucid style, the fundamental concepts of allergy and of its component clinical groups. In the section on hay fever she has provided, through the contribution of O. C. Durham, comprehensive charts and maps showing the distribution of important hay fever-producing pollens and the areas where they may be avoided.

In the section on bronchial asthma, many practical suggestions for ridding the home of causative factors are given. A brief discussion is included of the medical and antibiotic agents found useful as countermeasures against asthma.

In the section on food allergy, the elimination diets of Rowe are included and many recipes are given in detail, which enable the patient to avoid his specific food antigens. The chapter on allergy of the skin should prove enlightening to the individuals suffering from this type of sensitivity.

In writing this volume, Dr. Sammis has furnished a satisfactory and practical aid to the physician who is faced with the task of explaining to his allergic patients the essential facts of their ailments.

W. C. S.

Enzymatic Concept of Anaphylaxis and Allergy and the Role of Eosinophils in Anaphylactic Reactions Related to Hormonal Alterations. Z. Z. Godlowski. Edinburgh and London, E. & S. Livingstone Ltd., 1953; Baltimore, Williams & Wilkins Company, 1953. Price, 15s. $3.50.

Ever since anaphylaxis was first described attempts have been made to understand and explain its basic mechanism. Anaphylatoxin was a name applied to the hypothetical substance, a toxin responsible for the symptoms of the shock reaction. Dale believed he had finally found it when histamine was discovered but histamine, and heparin too, for that matter, released as a result of antigen contact with sensitized cell have never been fully accepted as the final and complete explanation.

The author, in the first chapter of the monograph under review, presents a theoretical discussion to explain anaphylaxis and allergy on the basis of enzymatic activity. In building up a basis for his thesis he introduces some new concepts on sensitization and its resulting reaction. On page 1, he says, "The anaphylactic phenomenon should be regarded rather as resulting from *the failure of the antigen-antibody reaction*," a statement which is not only bold but completely unorthodox. Dr. Godlowski then proceeds "to give a brief description of the nature and mode of action of antigen and antibody and of the mechanism of sensitization and anaphylactic shock" as he conceives it. The outline of the hypothesis is best described in his own words as follows: "Sensitization is a condition in which toxic enzymes appear in the cells involved as a result of antigenic action. Antigen may therefore be described as any substance which when introduced into the animal organism, whether orally or parenterally, is able to induce the formation of: (1) a toxic enzyme system in the cells liable to be sensitized and (2) specific antibodies in the tissues concerned. These two fundamental features of antigen are not necessarily coupled with each other, i.e., the production of specific antibodies may take place in an organism in which sensitization has not occurred and vice versa."

Another, so far as I am aware, novel idea is presented in the statement that antigenic proteins may be incorporated into the host cell and "may or may not alter the whole character of these cells. Furthermore, this physiopathological state may be transmitted to the next generation according to the Mendelian Law."

The author develops the concept of enzyme activity by the assumption of several proteolytic enzymes, those normal to the organism which hydralize protein, antigenic or nonantigenic, to the level of nontoxic catabolites, then there are specific proteolytic

enzymes (antibodies) which act only on antigen and reduce it to nontoxic substances, and, finally, a third type "specific proteolytic toxic enzymes" whose formation constitutes the basic phenomenon of anaphylactic sensitization and the products of whose activity creates the toxic catabolites of the shock reaction.

Naturally the analogy of peptone shock is used to support the author's thesis of toxic protein split products but nowhere does one find, in the first chapter, any evidence as a result of his own work nor that of any other research scholar. In short, this chapter of the book is acceptable only as an interesting presentation of pure hypothesis without the merit of factual support for the presence of the toxic enzymes nor their toxic catabolites.

Another chapter deals with the role of eosinophils in anaphylaxis. The author has carried out interesting investigations and supports his histologic findings with excellent color plates; but again the discussion becomes largely speculative. He regards eosinophils as "carriers of antigens" and cites them as "examples of isolated cells which have developed a new function—that of synthesizing foreign protein." In fact, the author states that "if large numbers of these cells [eosinophils] are destroyed their antigenic proteins may be liberated in sufficient amounts to precipitate an anaphylactic reaction," although he believes this is rare.

It is hoped that the author will continue his studies to develop support for his thesis. This is not the first time that enzymes have been discussed in relation to the immunity and anaphylaxis. I am reminded here of the publication of Sevag in 1945 entitled *Immuno-Catalysis,* a book replete with experimental facts indicating the relationship of enzyme and antigen.

Godlowski's book is not one that adds to our knowledge and is not one for the immature student of immunology but it may afford interesting discussion and speculation among the seasoned immunologists and enzymologists.

It's Not All in Your Mind. H. J. Berglund, M.D., and H. L. Nichols, Jr., Greenwich, Conn., North Castle Books, 1953. 343 pp. Price, $3.95.

This volume is dedicated "to those who suffer and die needlessly because of ignorance and false information," presumably because their allergic diseases are falsely attributed to psychosomatic causes. Some physicians may question whether the lay public is in a position to judge whether more damage is done by mistaking organic for psychosomatic disease or vice versa. However, the psychoanalysts and other psychosomaticists have been so prolific in selling their approach directly to the laity by books and magazine articles that the occasional voice raised in rebuttal deserves some sympathetic listeners. As the author states, asthma in particular has been one of the chief targets of the "It's all in your mind" school, and probably more nonsense has been spoken and written about it than any other disease. Obviously the real solution depends not so much on appeals to the laity as on better education of the general practitioner and a broader background of general medicine for the physicians who undertake highly specialized methods of medical or psychiatric treatment.

Those who welcome such a book will regret that the immunologic concept of allergy has not been presented by a more widely known or at least a more conventional advocate. Many views expressed as fact lack adequate proof and serve to weaken the force of the book. For example, the claim that allergy can usually be demonstrated by a count of the white blood cells and by precipitin tests for antibodies is hardly more acceptable to most allergists than psychiatric theories of asthma. The concept of aggravation of asthma by exertion as a form of heat allergy brought on by an increase of body temperature certainly requires physiologic investigation. The bounds of allergic disease are stretched to include arthritis and "shifting pains," not on the basis of immunologic evidence, but because cures are produced by desensitization with mold-bacterial vaccine. Admittedly the field of allergic dermatitis is confused at present, but one reads with surprise the charge that "a clique of eastern dermatologists" has not only rejected the

view that foods may cause dermatitis but has even suppressed discussion of the subject at medical meetings. Possibly the greatest surprise is the concept of the body fat of modern civilized man as a vast storehouse of D.D.T. constantly adsorbed from contaminated food and apt to produce toxic symptoms if mobilized by weight reduction. A good deal of standard material on allergy is intermingled with these more exotic views, but it is hard to avoid the impression that one who throws stones at the psychiatrists should have his own windows better shuttered.

Atlas of Regional Dermatology. Ernest K. Stratton, M.D. Springfield, Ill., Charles C Thomas, 1953. 288 pp. Price, $15.

Whether willingly or not, the allergist is apt to be confused with the dermatologist and see a variety of skin lesions of obscure etiology which patients or their physicians vaguely hope may be amenable to the allergic approach. If he is to avoid being misled, some knowledge of the differential diagnosis of these conditions is essential. Most available textbooks of dermatology contain a great deal of material on treatment subjects not of interest to the physicians interested primarily in differentiating the allergic and nonallergic dermatoses. The present volume, with 596 illustrations, 25 of them in color, should help to fill the need of allergists.

The illustrations are arranged according to the locations of the lesions with conditions of similar appearance presented together, so that the diseases to be differentiated are readily apparent without reference to the index. Throughout most of the book the illustrations are accompanied by brief notes on differential diagnosis, but at times the text is completely lost in the abundance of photographs, leaving the reader in a confusion of the obscure Latin names so common in dermatology.

The choice and reproduction of photographs is excellent, but the few colored plates are so much more revealing that they necessarily make the black and white seem inadequate by comparison. On the whole the book can be recommended for those needing aid in the identification of skin lesions.

Obituary

CHARLES KORAN MAYTUM died April 10, 1953, at his home in Rochester, Minn., after a long illness, of coronary sclerosis.

Dr. Maytum was born Dec. 20, 1895, at Alexandria, S. D. He attended the University of South Dakota from 1913 to 1915 and received the degree of M.D. in 1919 from the State University of Iowa College of Medicine. He interned at the Cincinnati General Hospital in 1919 and 1920 and was resident physician the following year. He was in practice at Alexandria, S. D., from 1921 to 1922.

Dr. Maytum entered the Mayo Foundation as a fellow in medicine in July, 1922, and was on leave of absence from Dec. 20, 1922, to March 6, 1923. He was appointed to the staff of the Mayo Clinic in 1926 and later became head of a section in the division of medicine. In 1927 he became instructor in medicine, Mayo Foundation, Graduate School, University of Minnesota, assistant professor in 1934, and associate professor in 1945. Later he became senior consultant, division of medicine, Mayo Clinic. During World War II, he entered the Medical Corps of the Army of the United States as lieutenant colonel and was promoted to colonel; he served from January, 1943, to October, 1945. He was chief of medicine of the 237th Station Hospital in New Guinea where he was stationed nineteen months. He was awarded the Bronze Star medal and the Asiatic-Pacific theater ribbon.

Dr. Maytum was certified in internal medicine and allergy by the American Board of Internal Medicine in 1937. He was a fellow of the American College of Physicians and a member of the Minnesota State Medical Association, the Southern Minnesota Medical Association, the American Medical Association, the American Academy of Allergy, the Alumni Association of the Mayo Foundation, Phi Rho Sigma, and Sigma XI.

W. B. B.